

DIPHtheria AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED  
MANUFACTURED BY LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.

1. Description. This product contains diphtheria and tetanus toxoids, adsorbed, combined with pertussis vaccine, and suspended in isotonic saline with 1:10,000 thimerosal added as a preservative. The diphtheria toxin and the tetanus toxin are detoxified with formaldehyde, and refined by the Pillemer Alcohol Fractionation Method, and adsorbed with aluminum phosphate. Phase I pertussis vaccine is prepared by growing the organism in modified Cohen-Wheeler Broth. A single 0.5 ml dose contains 12.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, and no more than 16 opacity units of Bordetella pertussis. Aluminum phosphate is contained in the final product at a concentration not greater than 0.8 mg per ml.

2. Labeling--a. Recommended use/indications. The package circular recommends this preparation for the simultaneous primary immunization of infants and children under 6 years of age against diphtheria, tetanus, and whooping cough, and for booster inoculations for this age group. Four 0.5 cc doses given intramuscularly are recommended, three doses at 4 to 6 week intervals with the fourth dose approximately 1 year later. A booster dose of 0.5 cc is recommended at 4 to 6 years of age (preferably at time of school entrance).

b. Contraindications. This product is not recommended for use in children over 6 years of age, nor for use in adults at any time. An acute febrile illness is considered an indication to defer immunization.

The labeling states that neurologic disorders in infants and children do not now appear to be a sufficient reason for withholding immunization. If an unusual neurological response to any given dose is observed, the physician is advised to proceed with caution using fractional doses of antigens or deferring immunization until the child is at least 1 year of age. Corticosteroids are mentioned as having an immunosuppressive effect, and it is suggested that a booster dose be given 1 month or more after such therapy is discontinued.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data regarding human immunogenicity or efficacy are provided in the submission. A number of reprints of reviews are included, all of which attest to the general safety and efficacy of DTP preparations in humans.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data regarding human safety are presented. References are made to the general body of knowledge supporting the safety of DTP products, but none provide specific data regarding the Lederle DTP, adsorbed product (Ref. 4a).

The manufacturer's marketing experience is listed in general terms only. In the past 5 years a few million doses of this DTP have been distributed. During that time, 62 complaints were received by the producer, but these are not detailed. It is noted that the main complaints have been pain on injection, local erythema, and febrile reactions in some instances including convulsions. No deaths are reported.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product when used for primary immunization cannot be determined with certainty, owing to the lack of human data on immunogenicity. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. Critique. The major problem apparent in a review of this product is the lack of satisfactory evidence for the immunogenicity of the diphtheria and tetanus components of this vaccine, when used in primary immunization.

The labeling is in general satisfactory, but should be revised and updated along the lines suggested by this Panel in the Generic Statement on Labeling.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization, and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years, during which time the manufacturer shall develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions in accordance with this Report are recommended.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED  
MANUFACTURED BY MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES

1. Description. This product consist of 10 Lf of diphtheria toxoid, 7.5 Lf of tetanus toxoid, 10 opacity units of thimerosal-killed pertussis bacilli suspended in culture supernatant, 1.0 + 0.35 mg of aluminum phospahte and 1:10,000 thimerosal in each immunizing dose of 0.5 ml. The pertussis component consist of 4 protective units per dose.

The pertussis vaccine is prepared from the growth of multiple Phase I cultures on the casein hydrolysate medium of Cohen and Wheeler.

2. Labeling--a. Recommended use/indications. The preparation is recommended for primary immunization of infants and children up to the age of 6 years. It is recommended that immunization start at the age of 2 to 3 months of age. Three intramuscular injections of 0.5 ml are given at intervals of at least 4 to 6 weeks. The third injection should be followed approximately 1 year later by a fourth injection to complete the basic series.

Reimmunization is recommended (0.5 ml) at the age of 4 to 6 years.

Emergency booster doses are recommended on serious exposure to pertussis if a booster dose of DPT has not been given within the preceeding year.

b. Contraindications. Any respiratory or other acute infection is reason for deferring injection. If marked or systemic reactions follow the first dose, subsequent doses should be decreased to 0.1 ml

and repeated every 4 weeks. If the child to be immunized has central nervous system abnormalities, the initial and subsequent doses should not exceed 0.1 ml per injection.

The risk of encephalopathic symptoms are described, but the package insert does not specifically advise that no further pertussis vaccine should be given if such symptoms occur after the first injection.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. McComb (Ref. 5) studied immune response in infants given 3 doses of Massachusetts Public Health Biologic Laboratories' DTP vaccine. Unfortunately no serological specimens were taken before immunization. More than 60 children were tested for diphtheria and tetanus antitoxin after immunization and all had titers in excess of 0.1 units. Eighty-four percent of 38 children under 2 years of age and 61 percent of children over 2 years of age had pertussis agglutinin titers of 1:320 and over after immunization. Provenzano (Ref. 6) studied 66 infants age 3 to 28 months who were given 3 doses of Massachusetts Public Health Biologic Laboratories' DTP vaccine. The geometric mean titer 3 months after injection was 109 agglutination units. Infants given more than 3 doses, including some plain pertussis vaccine, had titers almost twice as high. Serological data from this study are presented in more detail by Levine (Ref. 7), including information on individual serological responses. (Eight of 48 children had no pertussis

agglutinin after the recommended schedule; the log titers varied between 1.6 and 2.8.)

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. In the study of McComb mentioned above, the rate of febrile reactions was less than 10 percent and that of irritability 7 to 13 percent. In the above mentioned study of Provenzano the rates of reactions also appeared acceptable.

c. Benefit/risk ratio. The benefit-to-risk assessment for this product is satisfactory.

d. Labeling. Labeling generally conforms to the Public Health Services Advisory Committee on Immunization Practices recommendations. The label should clearly state that should a child experience convulsions, shock, encephalopathy, or thrombocytopenia following an injection of DTP, he should receive no further pertussis vaccine, but subsequent immunizations should be given with DT only.

4. Critique. A multitude of published studies demonstrate the efficacy of this product. The package insert does not define the risk of giving additional pertussis vaccine to a child who has previously had a severe reaction to pertussis vaccine.

5. 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 should be revised in accordance with the recommendation of this Report.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED  
MANUFACTURED BY MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC.

1. Description. This manufacturer maintains a single license for 2 preparations of diphtheria and tetanus toxoids and pertussis vaccine. The first, apparently the older of the 2 products, is prepared by precipitating all 3 antigens with alum prior to combination, and contains 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, and 12 opacity units of pertussis vaccine per 0.5 ml dose. The second product is prepared by combining diphtheria and tetanus toxoids, adsorbed onto aluminum phosphate, with pertussis vaccine. This preparation contains 15 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid with 12 opacity units of pertussis vaccine per 0.5 ml dose. Each preparation contains 4 protective units of pertussis vaccine per dose.

2. Labeling--a. Recommended use/indications. The recommendations for the use of these 2 preparations differ slightly from each other, but both are acceptable by the standards of current immunization advisory groups. For each, 0.5 intramuscular doses are recommended, beginning before 2 months of age and separated by at least 1 month. Reinforcing doses are recommended 1 year later and between 3 and 5 years of age.

b. Contraindications. It is recommended that further injections of the preparation not be given if a neurologic reaction to the vaccine occurs. It is also recommended that elective immunization be deferred during an epidemic of poliomyelitis. The recommendations for the alum

precipitated preparation are dated nearly 17 years ago and those for the aluminum phosphate adsorbed preparation nearly 14 years ago.

3. Analysis--a. Efficacy--(1) Animal. These products met Federal requirements when manufactured.

(2) Human. Data are not available.

b. Safety--(1) Animal. These products met Federal requirements when manufactured.

(2) Human. These products were marketed for nearly 12 years through 1964, during which time many million doses were distributed. There were 132 reports of reactions, none of which was said to be significant.

c. Benefit/risk ratio. The benefit-to-risk assessment cannot be determined in the absence of efficacy data in humans.

4. Critique. This combined diphtheria and tetanus toxoid and pertussis vaccine is apparently licensed in 2 forms, 1 of which is alum precipitated, and the other of which is aluminum phosphate adsorbed. Neither has been marketed since 1964. Efficacy data related to this product are not available.

5. Recommendations. The Panel recommends that these products be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because these products are not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE MANUFACTURED BY  
MERRELL-NATIONAL LABORATORIES, DIVISION OF RICHARDSON-MERRELL INC.

1. Description. This trivalent fluid vaccine contains, per each 0.5 ml dose, 10 Lf of diphtheria toxoid, 2 Lf of tetanus toxoid, not more than 20 opacity units of pertussis vaccine, and 1:10,000 thimerosal as a preservative, suspended in isotonic saline. Each dose contains 4 protective units of pertussis vaccine.

2. Labeling--a. Recommended use/indications. This product is recommended for the active immunization of infants and young children against diphtheria, tetanus and pertussis simultaneously. Three intramuscular doses of 0.5 ml each are recommended at 4 to 6 week intervals beginning at age 2 or 3 months with a reinforcing dose 1 year later. The manufacturer does not specify preference for the fluid or adsorbed product.

b. Contraindications. An acute illness is considered reason to defer immunization with this product. It is also recommended that routine immunization with this product not be given if the child exhibits a personal or family history of central nervous system disease or convulsions. There is also a warning about immunization during an epidemic of poliomyelitis. The occurrence of any type of neurologic symptom or sign following the administration of this product is considered an absolute contraindication to further use.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No human efficacy data are available for this trivalent fluid vaccine.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Six reports of adverse reactions, all of minor consequence, were received by the manufacturer during a 5 year period when many hundred thousands of doses of this vaccine were distributed.

c. Benefit/risk ratio. The risk from this product appears to be minor; in the absence of human efficacy data for primary immunization the benefit-to-risk assessment cannot be determined with precision. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. Critique. This combined fluid preparation for immunization against diphtheria, tetanus and pertussis appears to meet Federal regulations for efficacy and safety in animals and appears to be safe for humans. However, data regarding its immunogenicity in man are not available.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization, and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years, during which time the manufacturer shall develop data regarding the efficacy of this product.

Labeling revisions in accordance with this Report are recommended.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED MANUFACTURED  
BY MERRELL-NATIONAL LABORATORIES, DIVISION OF RICHARDSON-MERRELL INC.

1. Description. This trivalent product for immunization against diphtheria, tetanus and pertussis contains, per each 0.5 ml dose, 6.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, and not more than 15 opacity units of pertussis vaccine, adsorbed with aluminum potassium sulphate. Each dose contains 4 protective units of pertussis vaccine.

2. Labeling--a. Recommended use/indications. This product is recommended for the active immunization of infants and young children against diphtheria, tetanus and pertussis simultaneously. Three doses of 0.5 ml each intramuscularly are recommended at 4 to 6 week intervals beginning at age 2 or 3 months with a reinforcing dose administered 1 year later.

b. Contraindications. An acute illness is considered reason to defer immunization with this product. It is also recommended that routine immunization with this product not be given if the child exhibits a personal or family history of central nervous system disease or convulsions. There is also a warning about immunization during an epidemic of poliomyelitis. The occurrence of any type of neurologic symptom or sign following the administration of this product is considered an absolute contraindication to further use.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The efficacy of this product was satisfactorily established by a 1950 study (Ref. 8) in which 100 infants were immunized and subsequently evaluated for the presence of immunity to diphtheria, tetanus and pertussis. Serologic responses were measured in 20 to 25 children for each of the vaccine components; all children studied had satisfactory responses to primary immunization.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. In the above mentioned 1950 study of 100 infants given more than 300 injections of this product no serious systemic or local reaction was observed. During the 5 years, 1968 through 1972; many million doses of this preparation were marketed, during which time 47 adverse reactions were reported. Four of these were serious, including 3 deaths, 1 of which was ascribed to an anaphylactic reaction. There was 1 case of encephalitis.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. This is a widely used trivalent preparation for immunization of young infants and children against diphtheria, tetanus and pertussis which appears to be associated with significant reactions very rarely and which has been shown to be efficacious in humans.

5. 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 revision in accordance with this Report are recommended.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE MANUFACTURED

BY PARKE, DAVIS AND CO.

1. Description. This product consists of a saline suspension of 12 protective units of pertussis vaccine (in three 0.5 ml doses) together with 50 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid per 0.5 ml dose in 0.9 percent saline solution with 0.01 percent thimerosal as a preservative. It is presumably derived from the same mixture of selected strains of Bordetella pertussis as are used in the monovalent fluid vaccine.

2. Labeling--a. Recommended use/indications. For immunization of infants against diphtheria, tetanus and pertussis starting at age 6 weeks to 3 months, give three 0.5 ml doses intramuscularly 4 weeks apart with a reinforcing dose 1 year later and a booster at age 3 to 6 years, or as a precaution in the presence of actual or potential exposure. For wound boosters the use of tetanus toxoid or tetanus diphtheria toxoid is preferred. (Mention of the possible use of this product for rapid immunization should be deleted.)

b. Contraindications. This product is contraindicated in the presence of thrombocytopenia. When a patient is on immunodepressant therapy immunization should be deferred.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data are presented.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Only market experience is cited which suggests no problem.

c. Benefit/risk ratio. The benefit-to-risk assessment appears to be satisfactory when used for booster immunization since this product is typical of a vaccine that has been widely and successfully used with no unusual incidence of reactions (but it should be noted that recent English studies suggest that reactions are fewer with the adsorbed vaccine). For primary immunization the risk appears to be low; data relating to the efficacy of this agent for primary immunization are not available and according to benefit-to-risk assessment cannot be established with precision.

4. Critique. This is a classical fluid DTP with no adverse data reported and a history of extensive marketing, but no quantitative data on reactions and limited data on marketing experience are provided. On the basis of official tests and general experience the product appears acceptable, provided human data on efficacy are furnished. The extremely high dose of diphtheria toxoid should be justified or modified.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization, and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued

for a period not to exceed 3 years, during which time the manufacturer shall develop data regarding the efficacy of this product. Labeling revisions in accordance with this Report are recommended.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED

MANUFACTURED BY PARKE, DAVIS AND CO.

1. Description. This product contains 4 protective units of pertussis vaccine, 15 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid per 0.5 ml dose. The antigens are adsorbed on aluminum phosphate in 0.9 percent saline solution. 0.01 percent thimerosal is added as a preservative.

2. Labeling--a. Recommended use/indications. This product is presented as providing efficient, convenient, and rapid immunization against the 3 diseases in question. Immunization is started at 6 weeks to 3 months with 3 doses of 0.5 ml each given 4 to 6 weeks apart and a reinforcing dose 1 year later. All injections are intramuscular. A booster is recommended at age 3 to 6 years or in the presence of actual or potential exposure, if 1 year or more has elapsed after the last dose.

b. Contraindications. Not recommended for children over 6 years, and should be deferred in children receiving immunodepressants or having acute illness. There is no mention of thrombocytopenia or encephalopathy as problems or contraindications.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The data provided by the manufacturer for its quadrivalent DTP poliomyelitis vaccine show satisfactory immunogenicity when used for primary immunization. Please refer to the review of the quadrivalent product.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. This product appears to be somewhat more reactive than might be expected (see Table 4 and section VC2 of manufacturer's data submission (Ref. 9)) but yardstick for evaluation is not apparent.

Reported reactions for market experience appear within reasonable limits.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. This is a classical adsorbed DTP which has been widely used with little adverse experience reported. It is prepared by well-established methods, tested for laboratory potency by a well-validated method and appears only slightly more reactive than the ideal preparation. It seems acceptable for release as safe and effective, although comparative reactive data would be desirable as would information on the significance of the strains used in the pertussis vaccine component.

5. 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.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS AND POLIOMYELITIS

VACCINES ADSORBED MANUFACTURED BY PARKE, DAVIS AND CO.

1. Description. This is a quadrivalent product containing per 0.5 ml dose 15 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, 12.5 opacity units of Bordetella pertussis suspension, and poliomyelitis vaccine, trivalent, antigenically equivalent to 1 ml of fluid poliomyelitis vaccine. The poliomyelitis component is prepared from Type 1, 2 and 3 poliovirus grown in monkey kidney tissue culture, and inactivated with formaldehyde and supplemental ultraviolet irradiation. Each dose further contains 32.5 mcg of protamine sulfate, 2.5 mg of aluminum phosphate, 0.0125 mg of benzethonium chloride as a preservative, and is adjusted to pH 7.0. A 0.5 ml dose further contains up to 0.00000025 units of penicillin, and 1 unit of streptomycin. The antibiotics are used in propagating polio virus for the manufacturing process, and are thus present in only trace amounts.

The protamine sulphate is apparently present in the vaccine as an aid to the aluminum phosphate adsorption. All 4 components of the vaccine are adsorbed on the aluminum phosphate.

2. Labeling--a. Recommended use/indications. This product is recommended for the primary immunization of infants beginning at an unstated age and children up to the age of 6, against diphtheria, tetanus, pertussis and poliomyelitis. An initial series of three 0.5 ml doses is recommended intramuscularly at 4 to 6 week intervals, followed by an additional dose of the quadrivalent product or poliomyelitis

vaccine alone after 6 to 12 months. If immunization was begun in infants under 3 months of age, four 0.5 ml doses are recommended in the initial series.

b. Contraindications. No absolute contraindications are listed. Local and febrile reactions are noted, and the labeling advises that in instances of marked reactions, immunization may be completed with monovalent antigens, and warns that if there are encephalopathic symptoms, further injections of products containing pertussis vaccine are contraindicated.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. There is extensive documentation of the immunogenicity of the quadrivalent product in humans. The first major clinical trial, reported by Barrett (Ref. 10) summarized the data obtained in the first major clinical trial. The lots used in this initial trial, however, were significantly substandard in potency of the pertussis component. Accordingly, a second major clinical trial was conducted in the years 1959 to 1960, using at various times both research and production lots of the quadrivalent product. These trials involved several hundred children, and a great deal of detailed data are provided to substantiate the immunogenicity in humans of all 4 components of this product.

In summary, there is substantial evidence of the human immunogenicity of all 4 components of this product when used as recommended.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. One study of the quadrivalent product is cited in the manufacturers submission (Ref. 11) which 851 children were studied, presumably in the course of primary immunization. There were 30 reactions possibly due to the immunization procedure, including 16 instances of tenderness at the injection site, 10 of fever, and 4 of rash. In the booster phase of the study, 6 instances of local or febrile reactions were reported. In another study of reactivity of the quadrivalent product, 50 children from Jamaica between the ages of 3 and 5 months were given an initial dose of 1 of 3 lots of this product. Although the criteria are not absolutely clear, 12 of the 50 children were described as having a significant local reaction, and 17 of the 50 children were described as having a significant systemic reaction. Eight children had erythema, 22 had induration, 11 complained of mild to moderate pain, none had severe pain, 19 had mild to moderate degrees of swelling and 32 had some fever during the first 48 hours. There were no severe reactions reported.

The submission (Ref. 11) further notes 4 instances of severe reaction, 3 of which included convulsions, reported during the years 1959 to 1963. A letter from a private physician, dated September 25, 1967, notes that physicians in the Boston area generally considered that the quadrivalent product had a higher frequency of minor reactions than was true of the trivalent product. In summary, however, adequate substantiation of the human safety of this product is provided.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. This product is unique in that analysis of the producer's submission presents a strikingly different set of problems from those encountered with other diphtheria-pertussis-tetanus products. The submission clearly provides satisfactory evidence of safety and immunogenicity when used for primary immunization in humans.

Nevertheless, the last lot of this product was released in the year 1968, and the labeling is by now strikingly out-of-date with current practice and recommendations.

There is little doubt that there is still a role for killed poliomyelitis vaccine in selected patients, but there is clearly not a major role as long as live oral poliomyelitis vaccine remains an accepted part of public health practice in the United States. This product therefore exemplifies an ironic circumstance in which there is adequate documentation of safety and efficacy, yet little if any use in preventive medical practice.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED  
AND POLIOMYELITIS VACCINE MANUFACTURED BY PARKE, DAVIS AND CO.

1. Description. This unique quadrivalent product was designed to solve the stability problem that developed when DTP and killed poliomyelitis vaccine were mixed together in a single vial. This product consist of a dual chambered disposable syringe, preloaded with 1 dose each of killed poliomyelitis vaccine and DTP, adsorbed. For maximum stability the 2 components are physically separated in the preloaded syringe.

The composition of the DTP component is the same as Parke-Davis Quadrigen. The poliomyelitis component is concentrated in a 0.3 ml dose, and contains 8.3 mcg of formalin, less than 0.0000005 units of penicillin, and less than 8.3 mcg of streptomycin. Benzethonium chloride 0.008 mg is added as a preservative.

2. Labeling--a. Recommended use/indications. Most of the labeling detailed the action of the preloaded double chambered bypass syringe. The recommended use and indications are otherwise the same as in the Quadrigen label.

3. Critique. All additional comments under labeling, analysis, critique and recommendations are identical to those in the Parke-Davis Quadrigen submission and review (Ref. 12). This product has similarly not been released since the year 1968, and all discussion and recommendations about Quadrigen apply with equal validity to this product.

4. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED

MANUFACTURED BY TEXAS DEPARTMENT OF HEALTH RESOURCES

1. Description. The product contains approximately 17.5 Lf of diphtheria toxoid and 10 Lf of tetanus toxoid, and not more than the equivalent of 16 opacity units of pertussis per each immunizing dose of 0.5 ml dose. The adjuvant is aluminum hydroxide, not to exceed 1.2 mg per ml and the preservative is thimerosal 1:10,000. The total human immunizing dose contains 12 units of pertussis antigen.

2. Labeling--a. Recommended use/indications. This preparation is recommended for all infants for primary immunization, starting at 2 to 3 months of age. The initial course consists of 3 intramuscular injections given at not less than 1 month and preferably not more than 3 month intervals, followed by a reinforcing dose given about 12 months following the third dose. Injections are to be given intramuscularly preferably into the midlateral muscles of the thigh or the deltoid. In children over 6 years of age, the single antigens or tetanus and diphtheria toxoids adsorbed (for adult use combined antigen) is preferred. A routine booster of DTP is recommended at 3 through 6 years of age. For exposure recall, the tetanus toxoid fluid is recommended.

b. Contraindications. Any respiratory or acute infection is reason for delaying immunization.

3. Analysis--a. Efficacy---(1) Animal. This product meets Federal requirements.

(2) Human. The decline of the morbidity curves for diphtheria, tetanus and pertussis in relation to introduction of vaccines in Texas is given as evidence of efficacy (Ref. 13). The Panel considers this evidence insufficient as proof of efficacy.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Since the introduction of this DTP vaccine in 1959 and the distribution of a few million doses, 17 reports of reactions have been received. The complaints have concerned fever but also contain the following report evidently from a single clinic: "High incidence of severe reactions; 20 to 30 percent of those immunized had severe reactions with cyst formation."

c. Benefit/risk ratio. The benefit-to-risk assessment of this product when used for primary immunization would be satisfactory if human efficacy is demonstrated and is satisfactory for booster immunization.

d. Labeling. The recommendations generally follow those of the Public Health Service Advisory Committee on Immunization Practices and are in general adequate except that there appears to be a misprint "tetanus and diphtheria toxoids absorbed" instead of adsorbed. The choice of fluid tetanus toxoid instead of adsorbed toxoid for exposure recall is questionable.

4. Critique. The major shortcoming is the lack of documentation of efficacy of this particular product, more specifically data on serologic response are lacking. The report of "20-30 percent of those immunized had severe reactions with cyst formation" (Ref. 13) requires some clarification.

Data on efficacy as reflected in serologic response are needed. Better observations could be made of vaccine reactions. Information on serological types of pertussis used in manufacturing may be of interest in view of recent data from Britain.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization, and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years, during which time the manufacturer shall develop data regarding the efficacy of this product. Labeling revisions in accordance with this Report are recommended.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED  
MANUFACTURED BY WYETH LABORATORIES, INC.

1. Description. This product is a combination of purified tetanus and diphtheria toxoids and killed Bordetella pertussis cells adsorbed on aluminum phosphate adjuvant. The pertussis vaccine is prepared from strains providing serotype antigens 1 through 6 grown on a charcoal-agar modification of Cohen-Wheeler medium. The bacteria are killed and detoxified by heating at 56° C for 30 minutes. Each 0.5 ml dose of vaccine contains 7.5 Lf diphtheria toxoid, 5.0 Lf tetanus toxoid and not more than 16 opacity units of pertussis vaccine. The preservative is thimerosal. The total human dose (1.5 ml) contains 12 antigenic units of pertussis vaccine.

2. Labeling--a. Recommended use/indications. This product is recommended for active immunization of infants and children through 6 years of age against diphtheria, tetanus and pertussis. Recommendations for dosage and administration follow Public Health Services Advisory Committee on Immunization Practices recommendations.

b. Contraindications. Defer use in acute respiratory infections or other active infections or during outbreaks of poliomyelitis. Immunization of infants with cerebral damage should be delayed until after 1 year and then single antigens in fractional doses should be employed. The occurrence of any type of neurological symptoms or signs after injection is said to be an absolute contraindication to further use.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data for this manufacturer's product were submitted. Claims for efficacy are based on citations of relevant literature for this type of product (Ref. 14).

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data dealing with this product were submitted. No reference to marketing experience or complaint file information was included.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product when used for primary immunization would be satisfactory if human efficacy is demonstrated, and is satisfactory for booster immunization.

d. Labeling. The labeling is adequate and straightforward. It has not been revised since 1970, and could perhaps be updated slightly although no serious problems exist.

4. Critique. The submission (Ref. 14) is lacking in specific information relative to human safety and primary immunogenicity of this manufacturer's product. There is no basis for immediate concern at this lack of information but it should be obtained in due course.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions in accord with this Report are recommended.

The Panel also recommends that data on the reactogenicity of this specific product be collected and made available to the Bureau of Biologics.

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GENERIC STATEMENT

Anthrax Vaccine, Adsorbed

Anthrax is an acute bacterial disease caused by Bacillus anthracis. The reservoir is any of several animal 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 for 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 nonproteolytic, 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 activity 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 goathair), bristles, and bone meal, as well as 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 is completed. If on 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 4 mills processing raw imported goat hair into garment interlinings. The study involved approximately 1,200 mill employees of whom about 40 percent received the vaccine and the remainder received a 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, 4 had incomplete immunization and 1 had complete immunization. Based on analysis of attack rates per 1,000 persons-months, the vaccine was calculated to give 93 percent (lower 95 percent confidence limit = 65 percent) protection against cutaneous anthrax based on comparison with the control group. Inhalation anthrax occurred too infrequently to assess the protective effect of 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; 3 were partially immunized (1 with 1 dose, 2 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 this 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 above studies 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 there is sufficient evidence to conclude that anthrax vaccine is safe and effective under the limited circumstances for which this vaccine is employed.

REFERENCES

- (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

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 sterile filtrate of 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 contract imported animal hides, furs, bone meal, wool, hair (especially goathair) 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 may suppress response. Further immunization should be discontinued in those rare individuals who suffer severe systemic reactions.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) 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 goathair. This vaccine appeared 93 percent protective (lower 95 percent confidence limit = 65 percent protective) against cutaneous anthrax. No meaningful assessment of its value against inhalation anthrax is possible due to its low incidence. The Michigan Department of Public Health vaccine is patterned after that of 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).

b. Safety--(1) Animal. This product meets Federal requirements.

(2) 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.

c. 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.

d. Labeling. The labeling seems generally adequate. There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24(a) defines a total primary immunizing dose as 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).

4. 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.

5. 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.

REFERENCES

- (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.

GENERIC STATEMENT

BCG Vaccines

Tuberculosis is a communicable disease of world-wide importance caused by Mycobacterium tuberculosis. The disease typically involves the lungs, but is capable of causing disease in any organ system of the body. The World Health Organization estimates the number of infectious cases of tuberculosis in the world today to be in the range of 15 to 20 million.

Tuberculosis has declined sharply in the United States during the past several decades. United States Public Health Service data indicate that in 1953 there were 84,000 new cases of tuberculosis and 19,700 deaths due to tuberculosis; in 1973 there were only 31,000 new cases, and the number of tuberculosis deaths had declined to 3,800. Factors contributing to the observed decline in tuberculosis morbidity and mortality include the gradual increase in socioeconomic level that has characterized the United States economy, improved nutrition, the introduction of effective chemotherapy of active tuberculosis, and the increasing use of isoniazid in preventive therapy. There remain, however, localized foci or "pockets" of tuberculosis transmission in the United States, particularly in areas in which preventive medical services are suboptimal or cannot be adequately delivered.

In many other countries, the use of BCG vaccine is credited with a major role in reducing tuberculosis morbidity. BCG vaccination has

been the major thrust of the World Health Organization's efforts to control tuberculosis in countries with high rates of transmission of the disease. Although available in the United States, this product has been used but little for the prevention of tuberculosis.

BCG vaccines posed a particular problem for the Panel, owing to the widely disparate results of controlled field trials, and the lack of a reproducible animal model which accurately reflects protective efficacy in humans.

1. Rationale for vaccination against tuberculosis. Earlier in this century, a large majority of people became infected with tubercle bacilli as demonstrated by skin test positivity. However, only a small porportion of those who were infected developed overt tuberculous disease. Most people who were infected appeared to have acquired a degree of resistance against developing overt tuberculosis upon subsequent exposure, which, earlier in this century, was frequent and virtually unavoidable.

Immunity in tuberculosis is now much more easily understood in terms of modern immunologic concepts, and the "unitary concept" of the pathogenesis of tuberculosis in man is generally accepted. Thus, primary infection with tubercle bacilli results in specific sensitization of host cell-mediated immune mechanisms, and is reflected clinically in the ability to elicit a positive tuberculin skin test. If the primarily infected person has received a large dose of tubercle bacilli, or if his cell-mediated immune mechanisms do not, for one reason or

another, respond optimally, the individual may go on to develop overt clinical tuberculosis. Most frequently, however, the tuberculous infection is localized by the host cell-mediated immune mechanisms, resulting in a dormant or latent infection which may (a) remain dormant for life, or (b) disappear and reactivate at some time in the future. Reactivation is frequently but not invariably associated with conditions known to impair host cell-mediated immune mechanisms, such as immunosuppressive therapy, certain malignancies, or malnutrition.

There is abundant clinical and experimental evidence that tuberculin positivity, reflecting activated cell-mediated immune mechanisms, is associated with protection against exogenous exposure to tuberculosis. Such individuals are, however, at risk of reactivation or "breakdown" tuberculosis. Tuberculin negative individuals are susceptible to primary infection, but by definition are not at risk of "reactivation" tuberculosis. The disease may be spread by individuals with primary infection, reinfecting susceptible individuals, or those with reactivation tuberculosis.

The use of BCG vaccine, an attenuated strain immunologically closely related to virulent Mycobacterium tuberculosis, attempts to gain the advantage of protection conferred by activated host cell-mediated immune mechanisms without risking progressive disease in man.

2. History of BCG vaccine. The bacillus of Calmette and Guérin, known as BCG, was originally derived from a virulent strain of Mycobacterium bovis, attenuated by 231 serial passages over a period of 13 years on

beef-bile containing medium. The early studies of Calmette and Guérin indicated that animals immunized with this culture developed increased resistance to a challenge dose of virulent tubercle bacilli. BCG vaccine was first administered by mouth to newborn infants in 1921. Since then the vaccine has been administered to more than 500 million persons of all ages.

The organism was maintained by serial passage at the Pasteur Institute, and in the decades following its description was subcultured and distributed to hundreds of laboratories in many countries. In those laboratories, many of which produced their own BCG vaccines, the strain was similarly maintained by serial subculture. It became apparent in the mid-1950's that serial subculturing in many different laboratories on differing media had resulted in the production, by inadvertent selection, of many different "daughter" BCG strains which differed, sometimes widely, in gross morphology, growth characteristics, biochemical activity, sensitizing potency, and even animal virulence. Nor was it possible, of course, to carry out direct comparisons of any of the BCG "daughter" strains to the original bacillus of Calmette and Guérin. In the last 2 decades most production laboratories have adopted a seed lot system, maintaining production strains in a lyophilized state, in an attempt to minimize the genetic variation that is unavoidable in serial subculture. The situation currently is thus that of many laboratories producing BCG vaccine, each using its own "daughter" strain, preserved in a seed lot system. The production strains are generally named by the city in which

the production laboratory is located, e.g., Paris, Copenhagen, London, Montreal, Rio de Janeiro, etc. Thus, there is no single BCG vaccine; there are, rather, dozens of different BCG "daughter" vaccines.

#### Description and Production of BCG Vaccine

The proper name of this product is BCG vaccine, and consists of a freeze-dried preparation containing live bacteria of the bacillus of Calmette and Guérin, an attenuated strain of Mycobacterium bovis. The strain must have been maintained in the form of a primary seed lot, the basic material from which secondary seed lots are prepared. Vaccine production may be either from primary or secondary seed lots. The source of the strain used in vaccine manufacture is not specified in current Federal requirements, which state only that the source of the vaccine shall be identified by complete historical records.

In most production laboratories, the bacilli are grown as a pellicle on the surface of liquid Sauton medium, or dispersed throughout Sauton medium. An early harvest, 6 to 9 days, is considered important for good survival after freeze-drying. After filtering and pressing, the semi-dry mycobacterial mass is homogenized at a controlled temperature, diluted, and subsequently freeze-dried.

Routine quality control carried out by production laboratories includes an identity test, test of contamination, safety test in guinea pigs, estimate of total bacillary mass by opacity and dry weight, viability determined by oxygen uptake, germination rate, or colony count, and tests of heat stability. Such routine tests are particularly important for insuring batch-to-batch uniformity.

The Panel is cognizant of the proposed new standards for BCG vaccine, as published in the FEDERAL REGISTER, Volume 39, Number 53, on Monday, March 18, 1974, pages 10158-10160. These standards define the necessity of demonstrating that production lots of BCG vaccine are incapable of producing progressive tuberculosis in guinea pigs, and induce tuberculin skin test positivity using 5 to 10 units of tuberculin purified protein derivative (PPD) in 90 percent of persons, previously tuberculin negative, given BCG vaccine. In addition to the clinical requirement for tuberculin skin test conversion, potency testing is required by a determination of the number of colony forming units, and the intradermal guinea pig test (Jensen's test).

Indications and Contraindications

This has long been a controversial issue in the United States. The recommended use of BCG vaccine is to prevent tuberculosis, but controversy has arisen when attempts were made to define the groups of individuals or populations that would benefit from BCG vaccination.

The recently published recommendations of the Public Health Service Advisory Committee on Immunization Practices with regard to BCG vaccines read as follows (Ref. 1):

"Thorough application of modern methods of case detection, chemotherapy, and preventive treatment can be highly successful in controlling tuberculosis. Nevertheless, an effective BCG vaccine may be useful under certain circumstances. In particular, BCG may

Benefit uninfected persons with repeated exposure to infective cases who cannot or will not obtain or accept treatment.

Specific recommendations--a. BCG vaccination should be seriously considered for persons who are tuberculin skin-test negative and who have repeated exposure to persistently untreated or ineffectively-treated, sputum-positive pulmonary tuberculosis.

b. BCG vaccination should be considered for well-defined communities or groups if an excessive rate of new infections can be demonstrated and the usual surveillance and treatment programs have failed or have been shown not to be applicable. Such groups might exist among the socially disaffiliated and those without a regular source of health care, possibly including some alcoholics, drug addicts, and migrants. Groups such as health workers who may be at particular risk of exposure to unrecognized pulmonary tuberculosis should, where possible, be kept under surveillance for evidence of newly acquired tuberculous infection. It must be recognized that only the occurrence of new infections reflects whether transmission is actually occurring."

In other areas of the world, particularly in those countries in which there is greater transmission of tuberculous infection within the population, BCG vaccination is practiced on a much wider scale. In highly endemic countries, vaccination of all newborn infants is recommended.

Unquestionably, BCG vaccine plays a major role in the control of tuberculosis in many countries of the world. In a country such as the United States, in which transmission of tuberculosis is at a low level, BCG vaccine may properly be viewed as an adjunct to tuberculosis control, supplementing methods of case detection, chemotherapy, and preventive treatment in those limited segments of the population in which an excessive rate of new infections can be demonstrated and the usual surveillance and treatment programs have failed or cannot be readily applied. Tuberculin-negative persons unavoidably exposed in other parts of the world to populations in which there is significant tuberculosis transmission might also benefit from BCG vaccine.

Since BCG is a live mycobacterial vaccine, it should not be given to persons with impaired immune response, particularly impaired cell-mediated immune mechanisms, such as occurs with certain congenital immunodeficiency states, lymphoreticular malignancies, sarcoidosis, or when immunologic response has been suppressed with corticosteroids, alkylating agents, antimetabolites, or radiation.

Although no harmful effects of BCG on the fetus have been observed, it is probably prudent to avoid vaccination during pregnancy unless there is an excessive risk of unavoidable exposure to infective tuberculosis.

Safety of BCG Vaccine

The early history of BCG vaccination was tarnished by the Lubeck catastrophe, in which 72 of 251 infants died of tuberculosis following BCG vaccination. That disastrous episode was subsequently shown to be due to contamination of the vaccine by a strain of virulent tubercle bacilli. Excluding, therefore, that episode the safety of BCG vaccine has never been seriously contested. Progressive disease has occasionally been reported in immunosuppressed hosts, particularly in hosts with defects of cell-mediated immune mechanisms. In a summary of the world's literature through 1968 only 13 fatalities were cited as due to BCG vaccination.

Efficacy of BCG Vaccination in Man

Table I presents, in summary form, the results of 8 controlled trials of BCG vaccination against tuberculosis. A strikingly wide range of efficacy is seen, ranging from 0 to 80 percent. Three trials, those in Georgia (1947), Georgia-Alabama (1950), and in Illinois (1947) showed no or very little effect. The Puerto Rico trial (1958) and the South India (1968) trial showed mild to moderate degrees of protection. Finally, the trial in North American Indians (1953), Chicago infants (1961), and the Medical Research Council trial in Great Britain (1972) showed excellent protection.

These trials vary in composition of study groups, age at vaccination, methods of vaccine administration and dosage, and origin of vaccine strains.

TABLE 1--RESULTS OF EIGHT CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS<sup>1</sup>

Population grp. and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of follow-up (years)	Vaccination group	No. of subjects		Cases of tuberculosis		Protective efficacy (%)	
						No.	Rate <sup>2</sup>	No.	Rate <sup>2</sup>		
	1935-1938				Unvaccinated	1	457	238	1	563	
North American Indians (8 tribes) (Stein & Aronson, (Ref. 2))	0-20 yrs.	Negative to 0.005 mg PPD-Seibert (250 TU)	Henry Phipps Institute, Philadelphia	9-11	BCG	1	551	64		320	80 <sup>3</sup>
	1937-1948				Unvaccinated	1	665	65		223 <sup>5</sup>	
Chicago infants, high-risk areas (Rosenthal, (Ref. 3))	Under 3 mths.	No initial tuberculin testing	Tice Lab. Chicago <sup>4</sup>	12-23	BCG	1	716	17		57 <sup>5</sup>	75

<sup>1</sup>Adapted from: British Medical Research Council (1972) Bulletin of the World Health Organization, 46:381.

<sup>2</sup>Annual rate per 100,000 population, usually allowing for losses from observations.

<sup>3</sup>The protective efficacy against death from tuberculosis was 82 percent for a period of 18-20 years (Aronson (Ref. 4)).

<sup>4</sup>This laboratory has issued a number of strains at different times and it is not known whether the strains used in these three trials were the same or not.

<sup>5</sup>Assuming a mean observation period of 17.5 years.

TABLE 1--RESULTS OF EIGHT CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS<sup>1</sup>--con.

Population grp. and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of follow-up (years)	Vaccination group	Cases of tuberculosis			Protective efficacy (%)
						No. of subjects	No.	Rate <sup>2</sup>	
	1947				Unvaccinated	2	341	3	11
Georgia, school-children (Comstock & Webster, (Ref. 5))	6-17 yrs.	Under 5 mm to 0.002 mg RT 18 (100 TU)	Tice Lab., Chicago <sup>4</sup>	20	BCG	2	498	5	17
	1947-1948				Unvaccinated		494	8	--
Illinois, School for mentally retarded (Bettag Ref. 6))	Adolescents & young adults	Negative in 1/1000 and 1/100 OT	Tice Lab., Chicago <sup>4</sup>	12	BCG		531	12	--

<sup>1</sup>Adapted from: British Medical Research Council (1972) Bulletin of the World Health Organization, 46:381.

<sup>2</sup>Annual rate per 100,000 population, usually allowing for losses from observations.

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TABLE 1—RESULTS OF EIGHT CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS<sup>1</sup>—con.

Population grp. and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of follow-up (years)	Vaccination group	Cases of tuberculosis		
						No. of subjects	Rate <sup>2</sup>	Protective efficacy (%)
	1949-1951				Unvaccinated	27 338	73	43
Puerto Rico, general population (Palmer Ref. 7))	1-18 yrs.	Under 6 mm to 0.0002 mg RT 19-20-21 (10 TU)	State Dept. of Health, NY	5-1/2 - 7-1/2 (mean: 6.3)	BCG	50 634	93	31 30
	1950				Unvaccinated	17 854	32	13
Georgia, Alabama, general population (Comstock & Palmer, Ref. 8))	5 yrs. & over	Under 5 mm to 0.0001 mg RT 19-20-21	Tice Lab., Chicago <sup>4</sup>	14	BCG	16 913	26	14 11

<sup>1</sup>Adapted from: British Medical Research Council (1972) Bulletin of the World Health Organization, 46:381.

<sup>2</sup>Annual rate per 100,000 population, usually allowing for losses from observations.

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TABLE 1--RESULTS OF EIGHT CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS<sup>1</sup>--con.

Population grp. and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of follow-up (years)	Vaccination group	Cases of tuberculosis		
						No. of subjects	Rate <sup>2</sup>	Protective efficacy (%)
	1950-1952				Unvaccinated	12 699	240	128
Great Britain, urban population (Brit. Med. Research Council Ref. 9))	14-15-1/2 years	Under 5 mm to 0,1 ml 1/100 Old Tuberculin (100 TU)	Statens Serum-Institut Copenhagen	15	BCG	13 598	56	78 28
	1950-1955				Unvaccinated	5 808	46	89
South India, rural population (Frimodt-Møller Ref. 10))	All ages	Under 5 mm to 5 TU RT 19-20-21	BCG Lab., Madras	9-14 (mean: 12.3)	BCG	5 069	28	52 61

<sup>1</sup>Adapted from: British Medical Research Council (1972) Bulletin of the World Health Organization, 46:381.

<sup>2</sup>Annual rate per 100,000 population, usually allowing for losses from observations.

<sup>3</sup>The protective efficacy against death from tuberculosis was 82 percent for a period of 18-20 years (Aronson (Ref. 4)).

<sup>4</sup>This laboratory has issued a number of strains at different times and it is not known whether the strains used in these three trials were the same or not.

<sup>5</sup>Assuming a mean observation period of 17.5 years.

Methods of case detection have been particularly variable, and become critically important in those trials in which the detected incidence of tuberculosis in the control group was already quite low. For example, the British Medical Research Council trials used intensive follow-up with chest films, whereas most American trials relied primarily on reports from health departments.

How can such widely disparate results be explained, if at all? Among suggestions that have been put forward are that the differences stem from nutritional or from genetic differences between the populations involved. The nutritional differences do not tally particularly well with the variations found in efficacy, and there is insufficient information available to assess whether genetic differences might be responsible. Three other possibilities merit serious attention.

First is the explanation for the poor results found in the Georgia-Alabama trials by Palmer (Ref. 7) and his colleagues. Palmer suggested that in areas where nonspecific tuberculin sensitivity was common, as is true throughout much of the Southeastern United States, a large proportion of the population had already acquired some natural immunity against virulent tuberculous infection from atypical mycobacterial infections. In this situation, vaccination with BCG would only supplement the immunity which already existed and would not make as large an apparent contribution as in an area which was relatively free from atypical mycobacterial infections. This hypothesis has been experimentally supported in guinea pigs, showing that infection with other mycobacteria did indeed

confer protection against subsequent virulent challenge. This protection, however, was always less than was conferred by BCG. Palmer suggested that this explanation could, at least in part, reconcile the widely differing findings of the Medical Research Council Trial in Great Britain and that in the Southeastern United States.

Hart (Ref. 11), however, subsequently showed that while differences in the frequency of other mycobacterial infections could well have contributed to this difference, it would scarcely be the whole story. He calculated that if none of the subjects in the Georgia-Alabama trial had any natural protection from other mycobacterial infections, the apparent efficacy of the vaccine in that population would have risen from the actual 14 percent to only 25 percent. Hart postulated that some other influence must be operating, and suggested as an inescapable conclusion that the vaccine used in the Georgia-Alabama trial must have been less potent than the Danish strain used in the Medical Research Council trial.

This is, then, the second possibility that merits attention; namely, that different products all labeled as BCG may differ widely in their immunizing effect, and that this could be the main reason, or even the only one, for the mutually contradictory results of different BCG trials. The manufacturer of the vaccine used in the Georgia-Alabama trial has also claimed that vaccine was administered by inappropriate technique.

At this date, it is difficult if not impossible to ascertain whether the vaccines or the technique of administration or both were responsible for the divergent results noted in controlled field trials. There is

independent evidence, however, that BCG strains used in vaccine production by the laboratory supplying vaccine for 2 of the field trials that showed no protection were very weak in terms of multiplication, allergenic potency, and protection in animals.

The third possibility is one recently suggested by Sutherland (Ref. 12). He has observed that areas with a high incidence of tuberculosis in the unvaccinated group showed a high efficacy of BCG vaccine, whereas those with a low incidence of tuberculosis in the unvaccinated group showed a low efficacy, suggesting that the efficacy of BCG may be greater in an area where there is much tuberculosis than in an area where there is only little. If this relationship is genuine, it suggests that superinfection of vaccinated subjects with virulent tubercle bacilli or other mycobacteria may be necessary to maintain the protection conferred by BCG vaccine. This concept is not without its parallels in other infectious diseases, but has not heretofore been suggested for tuberculosis and BCG vaccine. A review of the 8 trials noted above demonstrates an association between the degree of protection and the degree of challenge.

All of the controlled field trials cited previously were carried out using liquid BCG vaccines. There have thus far been no field trials of freeze-dried BCG vaccines reported, though 1 is currently in progress in India. To date the only evidence supporting the efficacy in man of freeze-dried BCG vaccine is extrapolated from uncontrolled experience. The results suggest, but do not prove, that the freeze-dried vaccine

prepared by Glaxo Laboratories is as effective in man as the liquid Copenhagen vaccine used in the Medical Research Council trial in Great Britain.

On the basis of presently available information, judgments concerning the safety and efficacy of BCG vaccines licensed for use in the United States must be made by inference from historical data plus whatever inference can be drawn from tuberculin conversion in man.

#### Special Problems

Marked differences in the immunogenic and sensitizing potency of BCG strains were demonstrated over 20 years ago. During continuous serial subculturing, the traditional way of maintaining strains prior to the introduction of seed lot systems, the emergence of mutant strains was unavoidable. Mutants that have a faster growth rate in vitro than do the parent cells can, in a relatively shorter period of time, emerge as the dominant strain. There have been striking spontaneous changes in such attributes as morphology, pigmentation, rate of growth, and even in the ability to protect animals against experimental infection. In the case of such marked phenotypic change, the "daughter" strain can no longer be regarded as the same as the parent strain. Seed lot systems have been used to preserve BCG strains for little more than a decade. Thus, there is no single scientifically defined entity known as BCG vaccine; there are rather many different BCG vaccines, with varied biological characteristics and almost surely varied immunizing potency in man. Such a state of affairs is, to say the least, highly undesirable.

Evidence concerning the relative merits of various established BCG strains is indirect, and derived largely from animal studies which are sometimes mutually contradictory. There is no doubt that strains differ widely in terms of virulence, and also in terms of protective efficacy in certain animal models.

The need for further strengthening of animal model systems was highlighted by the recent report of Wiegeshaus (Ref. 13) and associates. In order to determine if the method by which a vaccine was tested was a major factor contributing to the results, an experiment was conducted in which a series of 5 different vaccines was distributed to each of 9 participating laboratories. Each investigator evaluated the potency of the vaccines in 1 or more animal models of his own choosing. This, in effect, held the method of vaccine preparation constant, while permitting all other variables to change. The ranking of the 5 vaccines was essentially random, thus demonstrating that the method by which the vaccine is tested in animals markedly influences its apparent potency.

Nevertheless, many authorities consider that there is some correlation between the potency of vaccine for animals and its protective potency for man. BCG vaccine with a high potency in animals may be expected to induce strong and long lasting protection against tuberculosis in man, whereas a vaccine with low potency for animals may be virtually worthless for vaccination of humans. Thus, it would seem reasonable to choose for the production of vaccine only strains that

are metabolically fully active, have good immunogenic potency in animals, and induce strong and lasting tuberculin sensitivity in humans.

One further controlled field trial of BCG vaccine is currently in progress in India, supported by the World Health Organization and the United States Public Health Service. This is the only controlled field trial of freeze-dried vaccines, and has utilized vaccines from 2 production laboratories at 2 dosage levels. This may well be the last opportunity to carry out well-controlled field trials of tuberculosis immunoprophylaxis, and the results will be awaited with considerable interest.

#### Recommendations

Public support should be made available for further development and evaluation of BCG vaccines in animal model systems, in order to provide models which are known to reflect protective efficacy in man accurately.

The results of the field trial currently in progress in India should be reviewed, when available, with particular attention to the adequacy of the scientific basis on which to recommend that all BCG vaccines distributed in the United States be prepared from the same seed lot strain of demonstrated efficacy in man.

#### Basis for Classification

The Panel considers that there is reasonable evidence of safety and efficacy of the 3 licensed BCG vaccines, and therefore recommends they be classified in Category I. This recommendation is not based on

unassailable evidence of the safety and efficacy of these individual products, but rather on the general totality of experience reported in previous field trials of BCG vaccines. The Panel arrived at its decision more by a consideration of the alternatives than by clear conviction that a Category I classification was fully deserved.

There is no evidence on which to classify these products as Category II unsafe and/or ineffective; although a classification in Category III was seriously considered. Given the lack of an animal model system directly correlated with efficacy in humans, such a classification would place an impossible demand on manufacturers to carry out controlled field trials of their BCG vaccines.

Therefore, the Panel recommends these products be placed in Category I, with the added stipulation that these products be reviewed again when the current World Health Organization-United States Public Health Service field trial in India is completed. If there emerges compelling evidence of efficacy of 1 or another BCG strain in that trial, subsequent review might well mandate United States licensed manufacturers to use that strain for vaccine production.

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SPECIFIC PRODUCT REVIEWS

BCG VACCINE MANUFACTURED BY CONNAUGHT LABORATORIES, LTD.

1. Description. This is a freeze-dried vaccine prepared from a strain of living attenuated bovine tubercle bacilli. The reconstituted vaccine for intracutaneous use is adjusted to contain between  $10 \times 10^6$  and  $30 \times 10^6$  viable cells per ml. Extensive details are provided of the manufacturing process itself. The origin of the Connaught Laboratories' BCG seed lot is presented in detail, and summarized as follows: Dr. Armand Frappier of the Institute of Microbiology and Hygiene of the University of Montreal received the strain on July 11, 1937, from Dr. Guerin of the Institute of Pasteur in Paris. It was apparently maintained in cycles of alternating 14-day passage on bile-potato medium followed by glycerinated-potato medium, followed again by bile-potato medium. A subculture was sent to Connaught Laboratories in April 1948 and the culture was thereafter maintained in cycles consisting of 5 consecutive biweekly passages on glycerinated-water-potato medium, followed by 1 passage on glycerinated-bile-potato medium for 2 weeks. The strain was lyophilized in 1967, when a seed lot system was introduced.

2. Labeling--a. Recommended use/indications. Under "selection of persons" in the package insert, the vaccine is stated to be given only to tuberculin negative individuals. It is recommended for use in the following groups of individuals.

All tuberculin negative individuals:

(1) Who by occupation are exposed to tuberculosis such as nurses, medical students and hospital attendants.

(2) Who are in the population groups or areas with high tuberculosis morbidity and mortality rates.

(3) With a known exposure to tuberculosis, or where an exposure may occur, as in the household contacts of patients with tuberculosis admitted to or discharged from hospitals or sanatoria.

b. Contraindications. It is said to be inadvisable to vaccinate individuals suffering from "general malaise" although that entity is not further defined, or intercurrent acute infections such as measles, whooping cough, eczema, or furunculosis. Caution is expressed that BCG vaccines should not be given with other antigens, and that there be sufficient time for reactions to either BCG vaccine or to other antigens to subside before vaccination is carried out with the other.

3. Analysis--a. Efficacy--(1) Animal. In experiments carried out in 1963 to 1965 (Ref. 1), when Connaught Laboratories was initially working with lots of freeze-dried vaccine, series of protection tests were carried out in both mice and guinea pigs using 3 vaccines, Glaxo Laboratories' freeze-dried BCG vaccine, a Connaught Laboratories' freeze-dried BCG vaccine and a Japanese freeze-dried BCG vaccine. In both mice and guinea pig experiments, the Glaxo Laboratories and Connaught Laboratories' products showed clear-cut evidence of protective efficacy in both mice and guinea pigs, whereas the Japanese freeze-dried product

produced no protection at all in mice, and was substantially less effective than the Glaxo Laboratories or Connaught Laboratories' products in guinea pigs.

The product meets Federal requirements. Current animal efficacy tests on lots of vaccine are apparently limited to a guinea pig potency assay, measuring only tuberculin skin test conversion.

(2) Human. No controlled studies of the efficacy of Connaught Laboratories' freeze-dried BCG vaccine have been conducted. There are several older studies in the Canadian literature showing the efficacy of a liquid vaccine prepared by Dr. Frappier, both in nurses and in newborns, but these data were not cited in the Connaught Laboratories' submission. Several studies of conversion rates have been carried out with the Connaught Laboratories' freeze-dried product, indicating that the Connaught Laboratories' product is comparable to other freeze-dried products in respect to producing very high skin test conversion rates.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The general body of world literature relating to the safety of BCG vaccine is cited in the submission to the Panel (Ref. 2) as evidence of safety of the Connaught Laboratories' freeze-dried product. The submission notes a few cases of post-vaccination abscesses and ulceration following Connaught Laboratories' BCG, but in each case these cleared up quickly and there was no evidence of tuberculosis.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. This is generally a thorough and complete submission from Connaught Laboratories. The information supplied by the manufacturer, the tests which this product is required to pass, and the general body of data concerning the safety and efficacy of BCG vaccines in humans are sufficient to place this product in Category I, in accordance with the discussion of this issue in the generic statement. The labeling is clear, but should be revised to reflect the current recommendations of the Public Health Services Advisory Committee on Immunization Practices.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

BCG VACCINE MANUFACTURED BY GLAXO LABORATORIES, LTD.

1. Description. This is a freeze-dried BCG vaccine, being a suspension of a living culture of a strain of the bacillus of Calmette and Guerin. It is prepared from a Glaxo Laboratories' substrain of the Copenhagen strain of BCG, dispersed in Sauton's medium with Triton, and cultured for 14 days at 37° C. The concentration is adjusted so that viability counts fall between  $4 \times 10^6$  to  $9 \times 10^6$  viable particles per ml for a low potency vaccine and  $8 \times 10^6$  to  $25 \times 10^6$  for a high potency vaccine for intradermal injection. Five  $\times 10^7$  to  $25 \times 10^7$  viable particles per ml of vaccine are used when the vaccine is intended for percutaneous administration.

2. Labeling--a. Recommended use/indications. The labeling is essentially a verbatim statement of the 1966 Public Health Services Center for Disease Control statement of the special panel of public health and tuberculosis specialists. This states, in effect, that BCG vaccine should be used only for the uninfected individual or small groups of uninfected individuals living in unavoidable contact with 1 or more uncontrolled infectious persons who cannot or will not obtain or accept supervised treatment.

b. Contraindications. BCG vaccine is contraindicated in tuberculin positive individuals. In addition, it should not be given to patients who are immunosuppressed, whether as a result of underlying disease or treatment.

3. Analysis--a. Efficacy--(1) Animal. There is general agreement that there is no animal test of potency of BCG vaccine known to correlate directly with protective efficacy in man. This is so stated in the Glaxo Laboratories' submission.

(2) Human. Several published works are cited in the submission to the Panel (Ref. 3) indicating the high skin test conversion rate when Glaxo Laboratories' freeze-dried BCG vaccine was used as directed. Additionally, the study of Springett and Sutherland (Ref. 4) is cited in which the efficacy of Glaxo Laboratories' freeze-dried BCG vaccine is retrospectively compared to the earlier experience in Birmingham when Copenhagen BCG vaccine in liquid form was used. In their analysis, the Glaxo Laboratories' freeze-dried vaccine performed just about as well as did the liquid Copenhagen vaccine. The authors point out that this was not really a controlled randomized trial, but rather a retrospective analysis using estimates of tuberculous experience in unvaccinated subjects. This is the only evidence, and indirect evidence at that, of effectiveness of any freeze-dried BCG vaccine.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. The work of the British BCG Control Center is reported in its entirety (Ref. 3), and provides substantial evidence of the safety of Glaxo Laboratories' freeze-dried BCG vaccine.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product appears satisfactory.

4. Critique. This submission appears quite adequate. The information supplied by the manufacturer, the tests the product is required to pass, and the general body of data regarding the safety and efficacy of BCG vaccine in humans are sufficient to place this product in Category I. The strain history is clarified, the Glaxo Laboratories' substrain being obtained from the Staten Seruminstitut in Copenhagen during the course of the Medical Research Council trial and immediately lyophilized. This culture has served as the master seed lot for vaccine production at Glaxo Laboratories since freeze-dried vaccine was marketed in 1957. The only remaining issue is whether the vaccine has retained full immunizing potency after freeze-drying and storage. The Panel believes that the retention of potency under these conditions is quite likely. (See discussion of this issue in the Generic Statement.)

There is no direct evidence that percutaneous vaccine is equal in protective efficacy to intradermal vaccine. One study (Ref. 5) is cited showing good comparability of tuberculin conversion rates when both routes were evaluated concurrently. In some recent studies, however, vaccine given by percutaneous multiple puncture methods has been less effective, as measured by skin test conversion, than vaccine given intradermally.

The labeling should be updated to reflect the current recommendations adopted by the Public Health Services Advisory Committee on Immunization Practices. Additionally, it would be of help to mention the size of needle to be used in intradermal injection.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

BCG VACCINE MANUFACTURED BY UNIVERSITY OF ILLINOIS

1. Description. This BCG vaccine is a freeze-dried preparation of a culture of the Calmette and Guérin strain of Mycobacterium bovis, prepared from a substrain of the Pasteur Institute strain and freeze-dried in lactose buffered salt solution. When reconstituted it contains  $1 \times 10^8$  to  $8 \times 10^8$  colony forming units per ml. A memorandum on the origin of the BCG strain used in the vaccine is included in the revised data submission from the manufacturer.

2. Labeling--a. Recommended use/indications. A package insert as such was not provided, but there is a 12 to 15 page document in the revised submission that appears to be a package insert. The vaccine is recommended as indicated for tuberculin negative persons who are exposed to risks of tuberculosis infection. No mention is made of medical or paramedical personnel, but some emphasis is placed on the desirability of BCG vaccine for children who live in, or plan to travel in, areas where tuberculosis is prevalent, or are in situations where there is likelihood of exposure to adults with active or recently arrested pulmonary or renal tuberculosis.

b. Contraindications. The vaccine is contraindicated in persons with a strong tuberculin reaction, fresh smallpox vaccination, or in burns. Severe immunodeficiency states, whether congenital, disease produced, or drug induced are also listed as a contraindication.

3. Analysis--a. Efficacy--(1) Animal. There is an extensive review of animal data in the submission to the Panel (Ref. 6), particularly in mice and guinea pigs, showing the protective efficacy of BCG vaccine in these animal systems, including data as recently as 1966 to 1970, relating to the current Tice product. It should be noted, however, that the efficacy of BCG vaccine in animal systems is not well-correlated with efficacy in humans.

(2) Human. The submission to the Panel (Ref. 7) provides an extensive review of both the controlled and uncontrolled studies carried out in the Chicago area from 1937 through the early 1950's. Some of this material has already been published. In the report by Rosenthal in 1961 (Ref. 8), there was good evidence that the vaccine was effective in reducing the rate of tuberculosis in children who had been vaccinated by a multiple puncture method at birth. Both liquid and freeze-dried vaccines were used.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Over the past 35 years, many thousands of vaccinations were performed using Tice vaccine. No fatalities have been directly attributable to BCG vaccine in the controlled field trials in Chicago. This is acceptable evidence of safety of this vaccine. In addition, the world literature attesting to the safety of BCG vaccine, as summarized by Mande, is noted (Ref. 9). Up to 1968, 13 fatalities have been reported as due to BCG vaccine, with probably over 500 million doses of BCG vaccine having been given.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product appears to be satisfactory.

4. Critique. The 1961 Rosenthal study (Ref. 8) is sometimes criticized as not being completely double-blinded, but overall it may be accepted as substantial evidence of efficacy of the vaccine. Studies carried out since that time have not been as well or at all controlled. There is, however, no mention in the submission of the several field trials using Tice vaccine which showed minimal or no protection. These include the Muscogee County Georgia study, the Georgia-Alabama study, and the Bettag study in an Illinois state school.

Nevertheless, information supplied by the manufacturer, the tests which this product is required to pass, and the general body of data relative to the safety and efficacy of BCG vaccines in man are considered sufficient to place this product in Category I, in accordance with the discussion of this issue in the Generic Statement. The labeling should be revised to include the current recommendation of the Public Health Services Advisory Committee on Immunization Practices.

5. Recommendations. With the exception of one panel member who recommended that this product be placed in Category IIIA, the Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

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GENERIC STATEMENT

Cholera Vaccine

Asiatic cholera is an acute diarrheal disease caused by Vibrio cholerae, which in its severe form, is characterized by a massive loss of fluid and electrolytes. If untreated, this disease may result in circulatory collapse and death within one day. In reality, such severe cases are the exception rather than the rule and epidemiological data indicate that for each severe case there are 25 to 100 mild to asymptomatic cholera infections. For the most part, significant epidemics are limited to areas with poor sanitation. The possible appearance of imported cases of cholera in countries with good sanitation is enhanced by transportation and increased international travel. Since 1960, the seventh recorded pandemic of cholera has extended westward from Southeast Asia across the Indian Subcontinent, the Middle East, into the African Continent, and into portions of Southern Europe. A small outbreak of cholera occurred in Louisiana in late 1978.

It is now well-established that the disease is produced by a heat-labile enterotoxin produced by Vibrio cholerae multiplying within the small bowel.

Infection follows the ingestion of water or food contaminated with human excretions containing Vibrio cholerae.

Highly satisfactory treatment of severe cholera is available consisting of prompt and adequate replacement and subsequent maintenance of fluid and electrolyte losses and correction of metabolic acidosis. Adjunctive antibiotic therapy (usually with tetracycline) results in

faster elimination of the organism and shortens the period of diarrhea. With prompt and adequate treatment, using intravenous and/or oral regimens, mortality is less than 1 percent. Unfortunately, adequate supplies of proper intravenous fluids and knowledge of treatment are often unavailable.

Immunization with cholera vaccine has been practiced for over 75 years, but no adequately controlled studies defining its relatively limited effectiveness were conducted until 1963. In the United States, the principal use of cholera vaccine is for military personnel and for individuals traveling to countries where cholera is endemic and/or where evidence of immunization is required. Although cholera is a quarantinable disease, under international health regulations, international certificates of vaccination for travelers from infected areas are no longer required in the United States and many other countries. In spite of the international health regulations and the total lack of any evidence that cholera vaccine prevents individuals from becoming carriers, some countries still require evidence of vaccination of travelers. The United States does not require vaccination of travelers from any country, and it is generally recommended that areas faced with an epidemic should not rely solely on vaccination but devote resources to provision of adequate treatment facilities, disease surveillance efforts and improvement of sanitation.

Nature of Product

Cholera vaccine, as licensed in the United States, is a bivalent whole cell bacterial suspension containing equal quantities of Ogawa and Inaba serotypes of Vibrio cholerae at a concentration of  $8 \times 10^9$  bacteria per ml. Only Ogawa and Inaba organisms of the "classical" biotype are employed since animal and field experience has shown that there is no advantage to the inclusion of organisms of the currently pandemic "El Tor" biotype which are antigenically identical and belong to either the Ogawa or Inaba serotypes.

Production

Organisms of the 2 serotypes are grown separately on agar, or in the case of 1 manufacturer, in a casein-hydrolysate broth. The bacterial count is standardized usually by opacity determination prior to addition of 0.5 percent phenol. The 2 serotype antigens are combined in equal amounts and diluted in 0.5 percent phenolized saline to a suspension of  $8 \times 10^9$  organisms per ml for the final vaccine.

Although 0.5 percent phenol is the only killing-preserving agent currently employed in licensed vaccines, formalin, mild heat, and organic mercurials also have been employed in other countries. No clear-cut advantage or disadvantage of any particular killing-preserving agent is discernible from available data in man.

The final vaccine is tested according to the United States standards. In addition to tests for sterility and general safety, the vaccine must be tested for nitrogen content, freedom from toxicity

(weight gain in mice), and antigenicity (protective activity in mice challenged intraperitoneally with each serotype suspended in mucin).

Use and Contraindications

This product is intended for active immunization against cholera. Primary immunization of adults has traditionally consisted of 2 subcutaneous or intramuscular injections of 0.5 and 1.0 ml respectively, given 1 week to 1 month apart. Reduced doses have been recommended for children 10 years of age or under. Booster doses are recommended every 6 months as long as the likelihood of infection exists.

In the light of published data now available (Ref. 1), no advantage is gained by the 1.0 ml volume for the second dose, and the recommended schedule can be restated as follows:

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Dose number	Intradermal* age (years) >5	Dose volume (ml) Subcutaneous or intramuscular age (years)		
		<5	5 - 10	>10
1	0.2	0.2	0.3	0.5
2	0.2	0.2	0.3	0.5
Boosters	0.2	0.2	0.3	0.5

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\*Higher levels of protection (antibody) may be achieved in children <5 years by the subcutaneous or intramuscular routes. In adults, somewhat lower levels of protection may be obtained by the intradermal route, but this route may be used as a means of minimizing reactions where a high level of protection is not necessary (e.g., most foreign travelers).

Absolute contraindications to the use of cholera vaccine are virtually nonexistent. Severe reactions have been reported but are extremely rare. As with other antigens, individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum response. Immunization should be withheld during febrile illnesses to avoid confusion as to the cause of further fever.

#### Safety

Immunization with cholera vaccine is generally accompanied by mild to moderate tenderness at the injection site, although more severe local reactions may occur occasionally. Such reactions may persist 2 to 3 days.

Local reactions may be accompanied in some instances by mild fever, malaise and headache. With adherence to the United States standards, excessive antigen content (i.e., significantly more than  $8 \times 10^9$  organisms per ml) should be largely eliminated as a cause of potential reactions.

Each batch of cholera vaccine must pass the standard Bureau of Biologics requirements for safety before it is released.

In summary, untoward reactions are not a major problem with cholera vaccine when properly produced and administered.

#### Effectiveness

Properly controlled field trials of cholera vaccines were first conducted in the early 1960's. Over subsequent years a series of field trials have been carried out in Bangladesh, the Philippines and India

(Ref. 2). A variety of vaccines, some experimental, have been tested and their apparent efficacy has varied widely, as have results from 1 trial to another. In general, protection in the range of 30 to 90 percent has been observed and has persisted for 3 to 6 months. However, in a recent study a monovalent vaccine of higher potency has shown good protection for as long as 3 years.

The seasonal nature of cholera complicates evaluation of the duration of protection, but protection is minimal or nonexistent with most vaccines in the subsequent cholera season (i.e., usually 1 year later). More prolonged protection has been observed in trials of an experimental oil adjuvant vaccine in the Philippines and with a fluid vaccine of high antigen content in Bangladesh. The oil adjuvant vaccine produced severe local reactions in the majority of recipients.

Field trials of monovalent vaccines in Bangladesh and the Philippines have shown that primary immunization with the Ogawa vaccine gave no protection against Inaba infection, whereas Inaba vaccine offered some cross-protection against Ogawa infection. These studies validate the need for bivalent vaccine because the infecting serotype often cannot be predicted.

Although no precise correlation can be established between potency as determined in the mouse and human effectiveness in field trials, a general relationship seems to exist (Ref. 3). The mouse protection test shows the same trend in cross-protection between serotypes as observed in field trials. The ability to stimulate vibriocidal antibody in

children is reasonably well correlated with vaccine potency determined in the mouse (compare Figures 3 and 4, (Ref. 3)). With bivalent vaccines, protection in man is correlated with acquisition of circulating vibriocidal antibody. Monovalent Ogawa vaccine stimulates vibriocidal antibody against the Inaba serotype, but fails to protect against Inaba infection, except perhaps in adults in endemic areas.

Therefore, the mouse protection test seems to be the most reasonable potency assay now available, although the disease in the mouse, a fulminating septicemia, bears no resemblance to cholera in man.

Although the vaccine prevents clinical cholera in approximately 50 percent of recipients for 3 months or longer, cost-effectiveness data indicate that cholera vaccination is of little value as a public health measure in combating a threatened cholera epidemic. Cholera vaccines do not interrupt transmission or prevent acquisition of the carrier state. It seems wiser to expend resources to improve diagnosis, to make available simple rehydration facilities (which are needed regardless of vaccination), to improve surveillance, to conduct health education programs, and, where possible, to improve sanitation. Unfortunately, few health authorities can resist the intense political and public clamor for mass vaccination programs which at best will offer limited protection to only a small segment of the population at risk, even in the rare instances when they can be efficiently carried out.

Special Problems

The major limitation of immunization against cholera with presently available vaccines is their inability to induce an efficient and durable immunity in the gut. Parenteral immunization does not seem to be an efficient means of stimulating the secretory immune system against cholera. Oral immunization with killed vaccines or live avirulent vaccine is a current research objective.

Recognition of the fact that Vibrio cholerae induces disease by production of a potent heat-labile enterotoxin (which is a classical exotoxin) has raised extensive interest. This antigen is not present in significant quantities in any available vaccine. A highly purified toxoid, detoxified with glutaraldehyde (because formalin-toxoid showed reversion), has failed to confer significant protection when administered parenterally in field trials in Bangladesh and the Philippines. It is possible that this antigen combined with the whole cell vaccine may have additive or synergistic effects, but this awaits future product development and field trial. Oral administration of toxoid is also being considered, in the hope of inducing secretory antibody. This assumes great importance, because available data from animal models clearly indicate the need for neutralization of the toxin before it can act on epithelial cell surfaces lining the gut.

Recommendations

1. The Panel recommends that public support for development of an improved cholera vaccine should be continued. Such support is necessary because unsatisfactory sanitary conditions in many countries, including

some in the Western Hemisphere, make it clear that control of the disease by sanitation alone cannot be realized in the foreseeable future.

2. Due to limited effectiveness of presently available vaccines, the Panel does not recommend that they be employed as a primary public health measure for mass immunization of populations threatened with cholera. The Panel recommends that the major efforts to control cholera comprise those of a sanitary nature and, in addition, include development of surveillance systems and provision of adequate facilities for diagnosis and treatment. Vaccine at present can be recommended for individuals who may visit countries which still require evidence of immunization beyond the current requirements of International Health Regulations. Cholera vaccine may also be prescribed as a secondary measure in the prevention of cholera in special circumstances for individuals or groups who need or may desire an additional measure of protection beyond that provided by sensible precautions in consumption of food and drink.

#### Basis for Classification

Because of the limited efficacy of cholera vaccine and the need for field trials in foreign lands for proof of efficacy, the Panel considered that the mouse protection test which has been well-correlated with efficacy, and fidelity to methods of well-established vaccine production are all that can be relied upon as a basis for classification.

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SPECIFIC PRODUCT REVIEWS

CHOLERA VACCINE MANUFACTURED BY ELI LILLY AND COMPANY

1. Description. The vaccine is a suspension of killed vibrio organisms prepared from the Inaba and Ogawa (equal parts) serotypes of Vibrio cholerae. The organisms are grown on nutrient agar, suspended in isotonic sodium chloride solution, and killed with 0.5 percent phenol, which serves as the preservative. The vaccine is standardized to contain 8,000 million organisms per ml. Total nitrogen content of the final vaccine does not exceed 0.05 mg nondialyzable nitrogen per dose.

2. Labeling--a. Recommended use/indications. The vaccine is recommended for active immunization against cholera. The dose is a single 0.5 ml injection subcutaneously or intramuscularly, but a second injection of 1 ml, presumably 1 month or more later, is recommended when unsanitary conditions may be encountered. Booster doses of 0.5 ml are indicated every 6 months if protection is needed. A reduced dosage schedule is recommended for children 5 to 9 years and a further reduction for children of 6 months to 4 years of age.

b. Contraindications. Vaccine should not be given during acute illness, convalescence from surgery or trauma, or in other conditions that would depress the immune response. The manufacturer cautions against simultaneous use of steroids, etc., during immunization and comments on their danger in the presence of exposure to infectious disease.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The submission (Ref. 1) cites various articles on the effectiveness of cholera vaccine in field trials. It fails to note that at least 1 of these trials was actually conducted with Eli Lilly and Company's cholera vaccine. The trial in question gave some of the best protection results observed to date.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. A large number of doses have been distributed in the last 5 years with only 11 complaints, 3 of which are presumably irrelevant.

c. Benefit/risk ratio. The benefit for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore, within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

4. Critique. Despite the generally modest evidence regarding any specific cholera vaccine, as well as cholera vaccines in general, this product is of relatively high acceptability when circumstances indicate its use. The label points out the shortcomings of cholera vaccine and is generally adequate. However, the importance of hygienic measures to control this disease should be pointed out in the package insert, which should also note the recent evidence suggesting that the second dose may be reduced to 0.5 ml. The lengthy discussion on corticosteroids in the face of infectious diseases is excessive and should be shortened.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

CHOLERA VACCINE MANUFACTURED BY LEDERLE LABORATORIES DIVISION,  
AMERICAN CYANAMID CO.

1. Description. Cholera vaccine is a bivalent mixture of Vibrio cholerae containing Ogawa and Inaba serotypes, each at a concentration of  $4 \times 10^9$  cells per ml (total count  $8 \times 10^9$  per ml). Lederle Laboratories Division's vaccine contains organisms grown in casein hydrolysate broth and killed and preserved with 0.45 percent phenol.

2. Labeling--a. Recommended use/indications. For active immunization against cholera. The recommended dosage consists of 0.5 ml and 1.0 ml injections 4 weeks apart with reimmunization every 6 months. No provision is made for reduced dosage for children.

b. Contraindications. Not recommended for use in the presence of acute infections.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data on immunogenicity of this product in man were provided. This particular product has not been employed in a controlled field trial, but is similar in potency to products which have been so evaluated and found to give modest protection (+ 50 to 70 percent) for 3 to 6 months.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Data from the manufacturer's complaint files revealed a very low rate of reaction complaints, all of a relatively minor nature.

c. Benefit/risk ratio. The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore, within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

d. Labeling. The labeling needs to be revised to correct 1 minor inaccuracy in that the United States Public Health Service no longer requires vaccination of travelers entering the United States from infected areas. In fact, cholera vaccine is no longer required by International Health Regulations, but a number of nations still unilaterally require it.

4. Critique. A field trial would be impractical for obvious reasons as previously discussed in this report. Vibriocidal antibody levels in recipients could be determined, but would be hard to interpret and would inevitably be seen with vaccines meeting United States standards of potency. The labeling fairly states the limited expectation for efficacy of such a product.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

CHOLERA VACCINE MANUFACTURED BY MERCK SHARP & DOHME, DIVISION  
OF MERCK & CO., INC.

1. Description. The manufacturer has provided very little material except to say that it contains 4 billion cells each of killed whole bacteria of the Inaba and Ogawa strains per ml. The diluent is physiological saline with 0.5 percent phenol.

2. Labeling--a. Recommended use/indications. No package insert is provided. However, the label states that 2 doses at 7 to 10 day intervals given subcutaneously are recommended, the first being 0.5 ml and the second 1.0 ml.

b. Contraindications. None is mentioned.

3. Analysis--a. Efficacy--(1) Animal. None is described.

(2) Human. None is described except reference to other studies. However, in the submission (Ref. 2) there is one reference to McBean, (Ref. 3) in which a few patients were given this preparation both subcutaneously and intradermally to compare the 2 routes. Apparently titers were satisfactory.

b. Safety--(1) Animal. This submission states that the bulk vaccine and the final product meets Federal requirements.

(2) Human. No evidence is provided.

c. Benefit/risk ratio. The benefit-to-risk assessment for this product cannot be determined because of insufficient information.

4. Critique. This submission is incomplete. Little or no information regarding efficacy is supplied, and the submission regarding animal safety is minimal. There are no data submitted regarding human

safety. Apparently this manufacturer is simply retaining his license but the product does not appear to be marketed.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

CHOLERA VACCINE MANUFACTURED BY MERRELL-NATIONAL LABORATORIES,  
DIVISION OF RICHARDSON-MERRELL INC.

1. Description. Each ml of vaccine contains  $8 \times 10^9$  killed Vibrio cholerae,  $4 \times 10^9$  Ogawa and  $4 \times 10^9$  Inaba strain, suspended in isotonic sodium chloride solution. The organisms are grown on agar and killed and preserved with 0.5 percent phenol.

2. Labeling--a. Recommended use/indications. To be used for active immunization against cholera. It is pointed out that immunization is mandatory for travel in many parts of the world. However, none of the shortcomings of cholera vaccine is mentioned.

(1) Adults. Initial injection of 0.5 ml; a second injection of 1.0 ml given 1 week to 1 month or more later. Booster injections: 0.5 ml every 6 months while danger of infection exists.

(2) Children. Two injections given 1 week to 1 month apart, in the following dosage according to age: 6 months to 4 years: 0.1 ml, 0.3 ml; 5 to 9 years: 0.3 ml, 0.5 ml; and 10 years and over: adult schedule.

(3) Booster injections. Give the same amount as the first dose indicated above every 6 months while danger of infection exists.

b. Contraindications. It is stated that "None known." Adverse reactions are mentioned.

3. Analysis--a. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Referral (Ref. 4) to the general literature only, with no information specifically for this product.

b. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. One study by Verway (Ref. 5) compares vibriocidal antibody responses among volunteers given either Cholera Research Laboratory vaccine (apparently manufactured by Eli Lilly and Company) or a vaccine from the National Drug Company. Since the National Drug Company's product is now the Merrell-National Laboratories' product, there are data in support of human immunogenicity for this product.

c. Benefit/risk ratio. The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

4. Critique. The labeling could be improved by mentioning that only 1 injection is required for international travel, although 2 injections may give somewhat better protection. The short duration of protection from cholera vaccine is not mentioned, although the need for booster injections is pointed out. Under contraindications it is merely stated that none are known, whereas the vaccine probably should not be given during acute illnesses and in persons who have previously experienced severe reactions to the vaccine.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

CHOLERA VACCINE MANUFACTURED BY WYETH LABORATORIES, INC.

1. Description. Each 1 ml of the vaccine contains not more than  $4 \times 10^9$  Vibrio cholera, serotype Inaba, not more than  $4 \times 10^9$  Vibrio cholera serotype Ogawa which has been grown on trypticase soy agar containing pancreatic digest of casein, soy peptone, and sodium chloride. The organisms are removed from the agar surface, suspended in 0.02 molar phosphate buffered saline, and phenol added to a concentration of 0.5 percent.

2. Labeling--a. Recommended use/indications. This product is recommended for active immunization against cholera. The recommended dose and intervals between doses are clearly delineated in the labeling.

b. Contraindications. Intercurrent active infection is listed as a contraindication to vaccination.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Nine controlled studies have been carried out in the Phillipines, Bangladesh and in India (Ref. 6). Vaccines of this type have shown from 39 to 83 percent protection. Mosley (Ref. 7) has demonstrated that a doubling of the mean vibriocidal antibody titer by active immunization was associated with a 50 to 60 percent reduction of the cholera case rate. It is not clear whether or not a Wyeth Laboratory preparation, per se, was used in any of these trials.

b. Safety--(1) Animal. This product meets Federal requirements.