

DIPHTHERIA AND TETANUS TOXOIDS ADSORBED MANUFACTURED

BY PARKE, DAVIS AND CO.

1. Description. This is an adsorbed combined diphtheria and tetanus toxoid which contains 15 Lf of purified diphtheria toxoid and 5 Lf of purified tetanus toxoid, adsorbed on 2.5 mg of aluminum phosphate per dose. The product contains 0.9 percent sodium chloride and 0.01 percent thimerosal.

2. Labeling--a. Recommended use/indications. This product is recommended for the primary immunization of children under 6 years of age when a triple vaccine is contraindicated or not recommended. The recommended schedule is 2 doses of 0.5 ml 4 to 6 weeks apart with a reinforcing dose of 0.5 ml about 1 year later. Recommendations concerning subsequent boosters conform with those of the American Academy of Pediatrics and the Public Health Service Advisory Committee on Immunization Practices. The recommendations regarding "wound boosters" are obsolete, as are the references; the package insert is dated 1970.

b. Contraindications. Acute febrile illnesses and courses of immunodepressant--including steroid--therapy are indications for postponing immunization. In addition, the insert recommends a Moloney test and an analogous test with tetanus toxoid before administering this preparation to children over 6 years of age. There is no mention of the use of adult-type tetanus-diphtheria toxoid for boosters.

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

(2) Human. Brief tabular summaries (Ref. 4) indicate that the product tested in 1961 to 1962 was satisfactory as a booster antigen, with what appears to be a relatively high reaction rate, primarily local (subjects were adults). No primary response data were presented.

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

(2) Human. The moderate to high reactivity mentioned above was observed in adults, hence, the acceptability of the product for children cannot be assessed.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product cannot be satisfactorily assessed, owing to the lack of data in support of the efficacy of this product when used for primary immunization in humans. The benefit-to-risk assessment of this product when used for booster immunization, is satisfactory. There was a higher rate of reactions in adults.

4. Critique. This product appears to be a typical combined diphtheria and tetanus toxoid product. However, data on the efficacy and tolerance of this product for primary immunization in the age group for which it is indicated are lacking.

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 should 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 be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

DIPHTHERIA AND TETANUS TOXOIDS ADSORBED MANUFACTURED

BY TEXAS DEPARTMENT OF HEALTH RESOURCES

1. Description. This product contains 30 Lf of diphtheria toxoid and 20 Lf of tetanus toxoid per ml; adsorbed onto aluminum hydroxide, the content of the latter not to exceed 1.2 mg per ml in the final product. It contains 1:10,000 thimerosal and the diluent is sodium acetate and buffered saline.

2. Labeling--a. Recommended use/indications. This preparation is recommended for immunization of children under the age of 6, or in children for whom there is a contraindication for combinations with pertussis vaccine. The dosage for primary immunization is 2 doses of 0.5 ml intramuscular injections at 4 to 6 weeks intervals followed by a third reinforcing dose 12 months later.

The skin should be cleansed with tincture of iodine and alcohol prior to immunization.

b. Contraindications. These include active respiratory disease or other active infections.

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

(2) Human. Only indirect data are provided (Ref. 5) demonstrating decreased incidence of tetanus and diphtheria in Texas relative to increased distribution of doses of vaccines for these agents.

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

(2) Human. The producer states that over the past 10 years many hundred thousand doses of the vaccine were distributed without any serious reactions being reported.

c. Benefit/risk ratio. If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. Labeling. The recommended use is in general agreement with the Advisory Committee on Immunization Practices recommendations. It would be desirable to have the Lf content stated on the label particularly as it is relatively high.

The recommendations for use of Td adult type for booster purposes is correct but easily misunderstood, since the name of the 2 products are almost identical: "tetanus and diphtheria toxoid, adsorbed (Td)" and "diphtheria and tetanus toxoid, adsorbed." Some of the labeling included in the manufacturer's data submission is illegible.

5. Critique. The manufacturer claims the product was patterned after that of the State of Massachusetts and thus controlled studies were not deemed necessary. However, the Lf content is considerably higher (15 Lf for tetanus toxoids, and 10 Lf for diphtheria) than what was used in Massachusetts at the time of this review (according to their submission, 7.5 Lf each of diphtheria and tetanus toxoid for the Massachusetts Public Health Biologic Laboratories' product). Furthermore, the Texas Department of Health Resources uses aluminum hydroxide, whereas

the Massachusetts Public Health Biologic Laboratories uses aluminum phosphate as adjuvant. Labeling regarding the product to be used for boosters is somewhat confusing. There are no human serological studies reported on this product, and the data on lack of reactions appear to be inconclusive.

6. Recommendations. The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should 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 be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

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

1. Description. This submission by Wyeth Laboratories includes an excellent summary description of the preparation of the 2 toxoids. The final product is a combined antigen product including in each 0.5 ml dose 10 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, and 0.34 mg of aluminum as aluminum phosphate. Sodium chloride is used to adjust tonicity of the final product.

2. Labeling--a. Recommended use/indications. This product is recommended for primary immunization and booster doses of infants and children through 6 years of age. The labeling clearly points out that in most instances a triple antigen (DTP) would be the preferred product. The labeling further differentiates very clearly between this preparation and the adult Td adsorbed preparation.

b. Contraindications. Acute active infection is listed as a relative contraindication, except in situations requiring emergency recall or booster doses. An outbreak of poliomyelitis is suggested as a reason to defer elective immunization.

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

(2) Human. The general body of data supporting the human efficacy of diphtheria and tetanus toxoids is cited (Ref. 6), but no data are provided regarding this particular product as currently produced by Wyeth Laboratories.

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

(2) Human. The general body of data regarding the safety of tetanus and diphtheria toxoids is cited, but no data are provided with regard to this specific product as currently produced by Wyeth Laboratories.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product when used for primary immunization cannot be precisely determined, owing to the lack of human data supporting its safety and efficacy. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. Critique. The labeling is clearly written, in conformity with current national recommendations, and clearly outlines the preferability of a triple antigen product. References to outbreaks of poliomyelitis as reason for deferral of elective immunization with adjuvant containing vaccines are probably no longer necessary.

The major defect in the submission is the lack of human data supporting the safety and efficacy of this product when used in primary immunization.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards the use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should 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 evidence regarding the efficacy of this product when used for primary immunization.

REFERENCES

- (1) BER VOLUME 2068.
- (2) BER VOLUME 2028.
- (3) BER VOLUME 2051.
- (4) BER VOLUME 2003.
- (5) BER VOLUME 2098.
- (6) BER VOLUME 2015.

GENERIC STATEMENT FOR TETANUS AND DIPHTHERIA

TOXOIDS (Td) FOR ADULT USE

See Generic Statement for Monovalent Diphtheria and Tetanus Toxoids

Description

Tetanus and diphtheria toxoids for adult use (Td) comprises a combination of tetanus and diphtheria toxoids in which the diphtheria component is significantly reduced compared to DT. The diphtheria component is reduced to avoid adverse reactions, such as fever and other systemic manifestations, in individuals who may have had repeated prior exposure to diphtheria antigens and have thus become sensitized to one or more of these antigens. All presently licensed products are adsorbed.

Production

Production of Td follows the same manufacturing procedures as for the individual toxoids and DT, with 2 major exceptions. The diphtheria toxoid component is reduced to a maximum of 2 flocculation units (Lf) per dose. Also, the purity of the diphtheria toxoid component for this product must be at least 1,500 Lf per mg of nitrogen. The Lf of the diphtheria component of currently licensed products ranges between 1.38 and 2 per dose.

Use and Contraindications

Tetanus and diphtheria toxoids for adult use is designed for 2 specific purposes. First, it is intended for use as a booster against tetanus and diphtheria in individuals older than 6 years of age, for the reason that it is not recommended to administer pertussis vaccine after this age, and because of possible prior sensitization to the

diphtheria toxoid component. In addition to its use as a routine booster, it is recommended for recall booster doses for the prevention of tetanus at the time of injury, at which time it would generally be useful to include enhancement of immunity to diphtheria.

The second purpose for which this combined product is recommended is that of the primary immunization of individuals older than 6 years. The usual recommendations are for the administration of 2 doses of Td at least a month apart, followed by a reinforcing dose approximately 1 year later and booster doses every 10 years thereafter, with appropriate intervening booster doses as recommended by national advisory committees, if injury or diphtheria exposure occurs. Contraindications are the same as for DT.

Safety

In accordance with Federal requirements both components of Td must be tested for detoxification prior to combination. These requirements are the same as for the individual components and for DT.

Efficacy

The diphtheria component must be tested for potency in animals prior to combination and both toxoids are tested for potency in animals after combination by specified techniques.

The immunogenicity of both components for man is satisfactory for boosters, but the adequacy of the reduced diphtheria component for primary immunization has not been established for all products. Neither

the diphtheria nor the tetanus component exerts a significant adjuvant or suppressant effect upon the immunogenicity of the other.

Special Problems

In addition to the problems of individual components (see Generic Statements on Individual Components), a major question is that of the immunogenicity of the smaller amount of diphtheria toxoid as a primary immunizing agent.

Recommendations

Because the same problems associated with the monovalent tetanus and diphtheria toxoids and DT apply to Td, the same recommendations apply with the exception of the issue of purity of the diphtheria toxoid.

In the absence of an animal or other laboratory model that can be interpreted with precision in terms of human immunogenicity, it is imperative that Td be studied in humans to ascertain its effectiveness as a primary immunizing agent against diphtheria.

Basis for Classification

The basis for classification of this combined product is the same as the basis for classification of the individual toxoid components.

BIBLIOGRAPHY

(1) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," Morbidity and Mortality Weekly Report, Suppl. 21(25):4-5, 1972.

(2) "Diphtheria - Tetanus - Pertussis," In Center for Disease Control, United States Immunization Survey: 1975, Health, Education, and Welfare Publication No. (Center for Disease Control) 76-8221:25-30, 1977.

(3) Center for Disease Control, "Reported Morbidity and Mortality in the United States 1976," Morbidity and Mortality Weekly Report, Suppl., Health, Education, and Welfare Publication No. (Center for Disease Control) 77-8241: 1977.

SPECIFIC PRODUCT REVIEWS

TETANUS AND DIPHTHERIA TOXOIDS ADSORBED (FOR ADULT USE)

MANUFACTURED BY ELI LILLY AND COMPANY

1. Description. 7.5 Lf of tetanus toxoid, plus 1.5 Lf diphtheria toxoid per dose in alum at a concentration of 2.55 mg per ml with 0.3 M glycine and thimerosal 1:10,000. The toxin is produced by growth of the organism in casein hydrolysate, and the toxoid is purified by the Pillemer process.

2. Labeling--a. Recommended use/indications. For primary immunization of adults and children 6 years of age or older against diphtheria and tetanus, two 0.5 ml injections are given 4 to 6 weeks apart and another 0.5 ml dose about 1 year later. Routine boosters are recommended every 10 years.

b. Contraindications. Children under 6; acute respiratory disease or other active infections (defer immunization). The labeling includes a cautionary statement regarding use of steroids and after exposure to infections, including tetanus.

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

(2) Human. No data were submitted to show evidence of immunogenicity for this product.

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

(2) Human. A total of 9 local and 7 systemic reactions have been reported over a 5 year period during which time many million doses were sold. This implies that the product does not have any unusual reactivity.

c. Benefit/risk ratio. If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. Critique. The major problem apparent in review of this product is the lack of evidence for immunogenicity for this specific product when used in primary immunization.

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 should 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 be expected to develop data regarding the efficacy of this product when used for primary immunization.

TETANUS AND DIPHTHERIA TOXOIDS ADSORBED (FOR ADULT USE)

MANUFACTURED BY LEDEKLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.

1. Description. This is an alcohol fractionated combined antigen preparation containing 5 Lf tetanus toxoid and 2 Lf diphtheria toxoid per 0.5 ml dose. It contains 2.5 mg per ml aluminum phosphate adjuvant and 0.01 percent thimerosal.

2. Labeling--a. Recommended use/indications. For active simultaneous primary immunization of adults and children over 6 years of age against tetanus and diphtheria and for subsequent booster immunization.

b. Contraindications. Acute respiratory diseases or other active infections. Should not be used under 6 years of age.

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

(2) Human. No data demonstrating the clinical potency of this specific product were presented. For this manufacturer's product (and similar products from other manufacturers), the suitability of the small 1 to 2 Lf dose of diphtheria toxoid for initiating primary immunization in very young children (beginning at age 7) is undocumented. Claims for efficacy are dependent on experience recorded in the literature for other products.

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

(2) Human. No specific data from detailed studies were presented.

However, general experience with this type of product is satisfactory, and the manufacturer has recorded a very low level of complaints from consumers.

c. Benefit/risk ratio. If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. Labeling. The statement (under "Precautions") which reads "It should NOT (except in extreme emergency when no monovalent toxoid or antitoxin is available) be used as a therapeutic agent," is ambiguous and should be corrected.

Since Td is the product specifically recommended for "wound booster" doses by the Public Health Service Advisory Committee on Immunization Practices (and other groups), some discussion of its proper use for this purpose alone or in combination with tetanus immune globulin (where appropriate) in tetanus prone wounds is needed.

4. Critique. The submission (Ref. 1) is lacking in data to support the use of this product in primary immunization, although it would be unquestionably adequate for booster use. It is especially important to document the suitability of the low dose of diphtheria toxoid for primary immunization of young children (7 and older).

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 should 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 three years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS AND DIPHTHERIA TOXOIDS ADSORBED (FOR ADULT USE)

MANUFACTURED BY MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES

1. Description. This product contains 4 Lf per ml each of diphtheria and tetanus toxoid, 4.0 mg per ml aluminum phosphate, thimerosal 1:30,000 with 0.01 M sodium acetate and 0.1 M sodium chloride as diluent, pH 6.0. Tetanus toxoid is grown on a modified Mueller medium.

2. Labeling--a. Recommended use/indications. This preparation is recommended for immunization of persons over 6 years of age. A total of 3 intramuscular injections of 0.5 ml each are recommended. Preferably there should be a 12-month interval between the second and third doses.

The product is also used for booster purposes, preferably at 10-year intervals. The recommendations are in general agreement with those of the Public Health Service Advisory Committee on Immunization Practices.

b. Contraindications. Acute respiratory diseases, and poliomyelitis epidemics. The concern with poliomyelitis epidemics may be deleted in the label in view of the rarity of such occurrence.

3. Analysis--a. Efficacy--(1) Animal. References to studies in animals of tetanus toxoid with the Massachusetts Public Health Biologic Laboratorie's products are given in the manufacturer's data submission to the Panel (Ref. 2). This product meets Federal requirements.

(2) Human. The Massachusetts Public Health Biologic Laboratorie's products have been tested in the field and data from the 1950's suggest that the recommended doses are highly efficacious as boosters. Also their efficacy in adults for primary immunization have been established in the paper by Ipsen (Ref. 3).

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

(2) Human. References in the submission to studies of reactions to toxoids made by Massachusetts Public Health Biologic Laboratories (Ref. 1) show acceptable low rates of reactions in the recommended doses.

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

d. Labeling. The labeling is adequate and up-to-date.

4. Critique. Sufficient evidence has been published to demonstrate efficacy and safety in adult use, in the past, both for primary and booster immunizations. Although this product was last tested more than a decade ago and the immune status of the general population may have changed since then with regard to naturally acquired immunity, it may not be possible to obtain more current information on primary immune responses to Td in adults in the near future.

5. Recommendations. The Panel voted after considerable discussion to assign this product to Category I on the basis of the older data with all due recognition of the possible limitations of the applicability of these data to the present day.

TETANUS AND DIPHTHERIA TOXOIDS ADSORBED (FOR ADULT USE)

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

1. Description This product contains 20 Lf of tetanus toxoid, 4 Lf of diphtheria toxoid, and 2.4 mg of potassium alum per ml in 0.3 M glycine, with timerosal 1:10,000.

2. Labeling--a. Recommended use/indications. No packaging insert is provided, no information is given regarding use, no actual labeling is provided (the photo of a label is illegible), and no useful information on the product is submitted.

b. Contraindications. No information provided.

3. Analysis. No data furnished.

4. Critique. The information furnished (Ref. 4) is totally inadequate for an evaluation of this product.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

TETANUS AND DIPHTHERIA TOXOIDS ADSORBED (FOR ADULT USE)
MANUFACTURED BY MERRELL-NATIONAL LABORATORIES, DIVISION OF
RICHARDSON-MERRELL, INC.

1. Description. This product contains up to 4 Lf of diphtheria toxoid and 10 Lf of tetanus toxoid per ml, adsorbed onto aluminum potassium sulfate and preserved with thimerosal in physiologic saline.

2. Labeling--a. Recommended use/indications. This preparation is recommended for the primary immunization of adults and children of 6 years of age or older. The dose is 0.5 ml given intramuscularly. For primary immunization 2 injections 4 to 6 weeks apart and a third dose 1 year later are recommended. A reinforcing dose every 10 years is recommended. The package insert contains no comment regarding reinforcing doses with injury.

b. Contraindications. These include acute illness and an outbreak of poliomyelitis in the community. It is noted that immunosuppressive therapy may interfere with response.

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

(2) Human. No information directly related to this product is available.

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

(2) Human. Over a 5 year period many million doses of this product have been distributed with a total of 8 reactions, most of which

appear to be minor. The only one of significance includes "paralysis," otherwise undefined.

c. Benefit/risk ratio. If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. Critique. This widely distributed product meets the United States standards for animal safety and efficacy and appears to be safe in humans. There is no information regarding its efficacy in humans, other than by analogy with other products. The package insert should include acceptable recommendations about emergency boosters. The inclusion of a community outbreak of poliomyelitis as a contraindication is probably unnecessary at the present time.

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 should 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 be expected to develop data regarding the efficacy of this product when used for primary immunization.

TETANUS AND DIPHTHERIA TOXOIDS ADSORBED (FOR ADULT USE)

MANUFACTURED BY TEXAS DEPARTMENT OF HEALTH RESOURCES

1. Description. This is a combined product containing, per 0.5 ml dose, 10 Lf of tetanus toxoid and 2 Lf of diphtheria toxoid, adsorbed onto aluminum hydroxide, with 0.01 percent thimerosal as the preservative.

2. Labeling--a. Recommended use/indications. This preparation is recommended for the primary immunization of children over 6 years of age and adults. The recommended course for primary immunization is 2 doses of 0.5 ml intramuscularly at 4 to 6 week intervals with a third dose approximately a year later. Subsequent reinforcing doses are recommended at 10 year intervals. There is no recommendation for a reinforcing dose on occasion of risk from diphtheria or tetanus.

b. Contraindications. It is recommended that immunization of individuals with acute respiratory disease or other active infection be deferred. It is stated that the product should not be used for treatment of active tetanus and that the product will not protect against tetanus when given at the time of injury unless the individual has been actively immunized previously. It is also stated that an optimum immune response cannot be expected in individuals receiving immunosuppressive drugs.

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

(2) Human. No data are available.

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

(2) Human. Several million doses were distributed in a 10 year period with no serious reactions reported.

c. Benefit/risk ratio. The benefit-to-risk assessment for this product when used for reinforcement of previously-established immunity is satisfactory. For primary immunization the risk appears to be low; data relating to the efficacy of this agent for primary immunization are not available and accordingly the benefit-to-risk assessment cannot be established with precision.

4. Critique. This combined, adsorbed diphtheria and tetanus toxoid preparation for the immunization of older children and adults would appear to be quite satisfactory for purposes of reinforcement of preexisting immunity. However, there are inadequate data regarding its efficacy for the primary immunization of such individuals.

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 should 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 be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

TETANUS AND DIPHTHERIA TOXOIDS ADSORBED (FOR ADULT USE)

MANUFACTURED BY WYETH LABORATORIES, INC.

1. Description. The Wyeth Laboratories' submission includes an excellent summary description of the preparation of the 2 toxoids. The final product is a combined antigen product, including in each 0.5 ml dose, 5 Lf of tetanus toxoid, 1.33 Lf of diphtheria toxoid, and 0.34 mg of aluminum as aluminum phosphate. Sodium chloride is added to the final product as necessary to establish isotonicity.

2. Labeling--a. Recommended use/indications. This product is recommended for primary and booster immunization of children over the age of 6 and adults against diphtheria and tetanus. The recommended number of doses and intervals between doses are consistent with recommendations of the Public Health Service Advisory Committee on Immunization Practices. The package insert emphasizes that this product should not be used for basic immunization or booster dosing in infants and children under 6 years of age.

b. Contraindications. Acute active infections are listed as a relative contraindication, except in the event that emergency booster dosing is required. An outbreak of poliomyelitis is said to be reason to defer elective immunization.

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

(2) Human. A recent report by McCloskey (Ref. 5) provides satisfactory evidence of the efficacy of Wyeth Laboratories' diphtheria and

tetanus toxoids, adsorbed (for adult use) when used as a booster dose. He boosted 123 adult hospital workers with Td toxoid, containing 1 Lf of diphtheria toxoid, and found no diphtheria antibody response in 21 percent of this group 1 month later. Their preimmunization titers for diphtheria antibody were less than 0.01 unit per ml, and all of those who failed to respond had either never been immunized against diphtheria or had been immunized more than 10 years prior to inclusion in this study. This data provided reasonable evidence of satisfactory human immunogenicity for the diphtheria component when used as a booster dose. No data were provided for the efficacy of this product when used in primary immunization.

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

(2) Human. Adequate evidence is presented in the report of Sisk and Lewis (Ref. 6) of the safety of Td toxoid, as prepared by Wyeth Laboratories, when used as a booster dose. No evidence of safety is provided for the use of this product in primary immunization.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product when used for primary immunization cannot be assessed with certainty, owing to the absence of acceptable data regarding its efficacy. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. Critique. The labeling is generally satisfactory. The labeling is well written, the recommendations for use are consistent with advisory bodies such as the Public Health Service Advisory Committee on Immuni-

zation Practices, and the indications for use of this product are clearly delineated. It is probably unnecessary to continue to refer to outbreaks of poliomyelitis as reasons for deferral of elective immunization.

The major defect in the submission is the lack of human data on the safety and immunogenicity of this product when used as a primary immunizing agent.

5. Recommendations. The Panel recommends that this product be placed in Category I as regards the use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should 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 evidence regarding the efficacy of this product when used for primary immunization.

REFERENCES

- (1) BER VOLUME 2029.
- (2) BER VOLUME 2054.
- (3) Ipsen, J., Jr., "Immunization of Adults Against Diphtheria and Tetanus," The New England Journal of Medicine, 251:459-466, 1954.
- (4) BER VOLUME 2010.
- (5) BER VOLUME 2017.
- (6) Sisk, C. W. and C. E. Lewis, "Reactions to Tetanus-Diphtheria Toxoid (Adult)," Archives of Environmental Health, 11:34-36, 1965.

GENERIC STATEMENT

Pertussis Vaccine

Pertussis, or whooping cough, is a bacterial infection caused by Bordetella pertussis (formerly Haemophilus pertussis) and is characterized by severe and paroxysmal coughing which persists for some weeks. The disease affects primarily infants and young children, and its morbidity and mortality rates are inversely related to age. Infants do not acquire adequate immunity from their mothers and are therefore highly susceptible to infection. The infection is localized in the respiratory tract, especially on the epithelial surfaces of the bronchial tree. The paroxysms of coughing ("whoop") are believed to be caused either by the tenacious nature of the secretions or conceivably by an effect of the disease process on the nervous system. Immediate complications include encephalopathy and convulsions, pulmonary atelectasis, and secondary infections such as pneumonia and otitis media. Developmental retardation and bronchiectasis may occur as permanent sequelae.

Pertussis responds poorly to treatment with antimicrobial drugs. Erythromycin and ampicillin, the 2 most commonly used antibiotics, are effective only if given in the earliest stages, although secondary complications caused by bacteria other than Bordetella pertussis usually respond satisfactorily.

In the United States, morbidity and mortality due to pertussis rapidly declined after increased utilization of pertussis vaccine in the 1940's and its official standardization in 1949, although the

disease persists as a significant contributor to infant mortality in developing countries. Indeed, the crude mortality rate from pertussis in this country decreased by 1967 to one two-hundred fiftieth of the 1930 rate; in 1973 only 5 deaths due to pertussis were reported. However, not all of this remarkable decline can be attributed to widespread use of the vaccine, for the reason that some decline in morbidity and mortality from pertussis was observed in the United States and other Western countries, prior to the institution of immunization. Nonetheless, the inference that part of the decrease is due to the vaccine is supported by an increase of pertussis in England where vaccine of low potency had been used. In addition, the disease has increased in countries, including Denmark, England and Japan where the use of vaccine was decreased because of the fear of severe reaction.

Despite these favorable mortality trends, pertussis is far from eradicated in the United States. The disease is ubiquitous although its incidence is low. The exact rates, however, are unknown for several reasons. Cases are frequently unreported or not recognized. Since verification of infection by isolation of the organism requires cultural methods not routinely used in many diagnostic laboratories, the infection may go undiagnosed. Further, serologic testing is not feasible for routine diagnosis. Infection in immunized persons may cause bronchitis but without typical whooping. Therefore, reports of pertussis obtained by the Center for Disease Control probably represent only a fraction of all pertussis infections occurring in the country.

The results of early studies of pertussis vaccines in the 1920's were encouraging, but far from satisfactory. Subsequent technical improvements in vaccine production included the use of freshly isolated and more immunogenic strains for vaccine production and later the testing of the potency of the vaccine by intracerebral challenge of vaccinated mice, a test that appears to correlate satisfactorily with the immunogenicity of the whole bacterial vaccine in children. Further, agglutination titers in the blood of vaccinated humans were found to correlate reasonably well with protection against disease. However, it should be noted that immunity achieved in man following the natural disease or immunization is not always absolute or permanent. Pertussis occasionally occurs in older children and adults with a history of prior immunization or infection.

Careful evaluation of several vaccines was conducted in Great Britain by the British Medical Research Council in the late 1940's and 1950's. Efficacy was estimated from home exposure rates, and the results showed that the most effective vaccines protected 90 percent or more of children from clinical disease. Vaccines lower in mouse potency were less effective. Other studies have also correlated the laboratory assayed potency with clinical efficacy.

Description

Current pertussis vaccine are aqueous preparations of either killed whole Bordetella pertussis bacteria or a fraction of Bordetella

pertussis bacteria. The vaccines may be fluid or adsorbed, and may be combined with other antigens.

In contrast to some other immunizing agents, such as diphtheria and tetanus toxoids, pertussis vaccine is a relatively crude preparation that contains the majority of the bacterial constituents, most of which are probably not relevant to the induction of immunity to the disease. The reason for this vaccine being impure is that the antigenic component of the bacterium responsible for clinical immunity has not yet been positively identified. There is 1 combined product presently licensed (a modified DTP) that contains a partially fractionated pertussis component and the relative efficacy of this product, compared to the whole bacterial pertussis vaccine, has not been determined in controlled field trials.

Production

Pertussis vaccine is made from cultures of 1 or more strains of phase I Bordetella pertussis that yield the required potency. The composition of the culture media must meet Federal regulations.

The bacteria are killed and detoxified by heating, addition of a chemical agent and appropriate aging, or an acceptable combination of these. The bacterial content must meet requirements specified in terms of the United States Opacity Standard. Vaccine potency is determined by comparing the results of the mouse protection test with that of the United States standard pertussis vaccine. A preservative, usually thimerosal, is added.

Federal regulations require that each lot of pertussis vaccine be tested in mice for immunogenicity prior to release. In this test, mice immunized with the vaccine lot are challenged intracerebrally with live organisms, and the results compared with those in mice similarly immunized with the United States Standard Pertussis Vaccine. The essential procedures for the test and its interpretation are specified in the Code of Federal Regulations.

The test provides a means of estimating the mouse potency of the vaccine lot. It must have a mouse potency of 12 protective units per total human immunizing dose, (3 doses) except that for the vaccine in the combined product containing poliomyelitis vaccine the potency may be no less than 14 units.

Use and Contraindications

Currently in the United States it is recommended that routine immunization begin at 2 or 3 months of age. Although monovalent pertussis vaccine is available, the trivalent product, with tetanus and diphtheria toxoids (DTP), is preferable. Earlier immunization may be undertaken if the disease is unusually prevalent in the community, but the immune response of very young infants is less satisfactory than that of older infants. The usual primary immunization schedule comprises the intramuscular administration of DTP on 4 occasions: 3 doses containing 4 protective units of pertussis vaccine each at 4 to 8 week intervals with a fourth dose approximately 1 year after the third injection. A booster dose, preferably at the time of school entrance, is recommended. Administration of pertussis vaccine is generally not

recommended after the age of 6 years because of the possibility of increased rates of adverse reactions and the fact that the disease is less severe in those 6 years or older, and because it has not usually appeared necessary for continuing protection. Rarely, in the presence of a community outbreak of pertussis, a booster dose of pertussis vaccine has been administered to older children and adults at risk, sometimes as a half dose (2 protective units).

An acute febrile illness is usually reason to defer immunization in order to avoid confusion as to the cause of subsequent fever and because of the possibility of an additive effect. The occurrence of an apparent severe reaction to the administration of any preparation containing pertussis vaccine requires consideration of modifying the subsequent dosage schedule. Significant reactions that have been attributed to pertussis vaccine have included high fever (greater than 39.5° C), a transient shock-like episode, excessive screaming, somnolence, convulsions, encephalopathy and, extremely rarely, thrombocytopenia. Such reactions almost always appear within 24 to 48 hours after injection, but have been thought to occur after an interval as long as 7 days. Shock, convulsions, encephalopathy, excessive screaming and thrombocytopenia, if believed by the physician to be due to the pertussis antigen, represent absolute contraindications to further administration of this vaccine. In the case of young children receiving combined preparations, immunization with the components of the preparation other than pertussis should be continued, usually as diphtheria and tetanus toxoids combined (DT). High fever and somnolence do not

represent absolute contraindications to continuing immunization against pertussis, but the physician should exert caution and may wish to consider fractional doses for subsequent injections.

Safety

Federal regulations require manufacturers to test each lot of vaccine for toxicity in mice prior to release. In this test, evidence of toxicity comprises failure of mice to achieve specified weight gain when injected intraperitoneally with one-half the single human dose. Different strains of mice may vary in their rates of weight gain and specifications for suitable test strains may be necessary. In addition to the toxicity test, each lot of vaccine must undergo a general safety test using animals and a sterility test. These tests are described in Title 21, Part 600, Code of Federal Regulations. In addition, it is expected that manufacturers keep records of all reactions in humans reported to them, and that these records be available to the Bureau of Biologics on request.

In spite of these precautions, untoward reactions to pertussis vaccine in humans occur. Low grade fever and local tenderness appear frequently after injection. The severe or disturbing untoward reactions, including shock, convulsions, encephalopathy, persistent high pitched screaming and thrombocytopenia, are rare complications, rates of which are difficult to define precisely, at least in part because they are often not reported. However, as morbidity and mortality from pertussis have declined, these reactions have drawn considerable attention. The frequency of fatal reactions has been estimated

to be 1 or 2 cases per 10 million injections in the United States. As with the neurologic complications of the disease, the mechanism of the untoward reaction is not understood. A responsible component in pertussis vaccine has not been identified, nor has any characteristic of vaccine recipients that predisposes to such reactions been found, although some observers have suggested that children with a history of convulsions are at higher risk. Observations in this and other countries indicate that vaccines of excessively high potency may be more reactive.

Pertussis vaccines adsorbed onto aluminum compounds elicit fewer adverse reactions and are thought to provide better and longer protection. The adsorbed vaccines are comparable to plain vaccines in the mouse weight-gain test and are approximately twice as immunogenic per bacterial content in the mouse potency assay. Pertussis vaccines potentiate the antitoxin response to diphtheria and tetanus toxoids, and thus it is advantageous to provide primary immunization to infants with a combination of pertussis vaccine and these toxoids (see Generic Discussion of DTP).

Efficacy

Studies reported by the British Medical Research Council in the 1950's showed good correlation of the mouse protection test results with clinical protection. Based on these results and those of other studies, the mouse potency test has been accepted as an indication of efficacy in lieu of field studies. In addition to the mouse protection test, agglutination titers in the sera of those vaccinated in the British

studies were found to correlate fairly well with efficacy. Agglutination titers of 1:320 or better were associated with protection in field studies. One notable exception was observed with a partially purified soluble antigen. This vaccine was found to be highly efficacious in terms of clinical protection but did not cause an agglutinin response except to the specific serologic strain that was used in the soluble antigen production. In other instances, it was observed that protection may sometimes exist in the presence of low agglutinin titers, but in general the presence of agglutinins seems to reflect immunity, though indirectly. Therefore the agglutination test may be used to evaluate vaccine potency when the incidence of the disease is too low for meaningful field studies of clinical protection, a situation that exists in the United States at the present time.

Later in the 1960's low efficacy of British vaccines was reported. Subsequent analysis attributed these failures to use of a standard vaccine that contained 2 instead of 4 protective units per single dose.

Protection from disease is directly related to interval since vaccination. The extent to which vaccination modifies the disease, rather than prevents infection, is unknown.

Although the immunogenicity of pertussis vaccine is less, and the reactivity higher than most other commonly used vaccines, all evidence supports the belief that the benefits of universal pertussis immunization considerably outweigh the adverse effects. The morbidity, mortality and neurological complications of immunizations are significantly less than those of the disease.

Special Problems

Although clearly of great value, pertussis vaccines do not exhibit the effectiveness and safety that have been achieved with certain other immunizing agents. Specific problems that deserve investigative pursuit may be grouped in 3 categories.

1. The pathogenesis of the disease and the biology of the organism are poorly understood. As a consequence, knowledge of the immune response and the mechanisms of complications of both the disease and immunization is limited.

It is not known what components of the organism are responsible for the clinical and pathologic features of the disease and its complications, or how they act. It is not known what component of the organism produces immunity, whether it is a single antigen, if it relates to the components that produce the disease characteristics, or whether it is identical to the mouse protective antigen. Further, the biologic attributes of the organism that produce the neurologic complications of the disease have not been identified, nor is it clear that they are the same as those responsible for the neurologic sequelae of immunization.

Current pertussis vaccines are complex mixtures of reactive cellular substances. Some progress toward identification of the mouse protective antigen has been made over the past 10 years. This component appears to be associated with the fimbriae and parts of the cell envelope. Whether the histamine-sensitizing and the lymphocytosis promoting factors can be separated from the protective antigen is unclear.

Until better definition of the components of the organism and their relation to disease and immunity are established, the effect of attempts to improve immunogenicity and reduce reactivity of pertussis vaccines by purification or extraction can only be evaluated by costly and logistically difficult field studies in humans.

2. The current epidemiology of pertussis and that of vaccine-induced complications are not defined with satisfactory precision.

As noted previously, reported cases of pertussis probably represent only a fraction of those occurring. Without adequate surveillance of disease rates, the effectiveness of current vaccines and immunization programs cannot be monitored.

Although there is evidence of worldwide shifts in the major antigenic characteristics of pertussis strains causing clinical disease, it is not known whether these shifts have diminished the effectiveness of pertussis vaccine. Changes in the distribution of serotype antigens in disease isolates from populations undergoing immunization have been demonstrated in several different geographic areas. These shifts in serotypes have prompted changes in pertussis strains used for vaccines in certain countries. However, experimental evidence indicates the serotypes are not necessarily protective moieties and the vaccine potency has not been related to these bacterial antigens. Studies that suggest an increase in pertussis in immunized children because of shifts in the wild organism cannot be interpreted because the protective unitage of the vaccines was not taken into account. However, there is no

firm evidence, as of now, that it is important to modify pertussis vaccines so that the immunizing strains reflect the strains prevalent in the community. This problem cannot be evaluated without better surveillance.

Experience with modern pertussis immunization is not of sufficient duration to predict whether childhood immunization may in some instances postpone natural infection until a later age. The disease itself does not always assure life-long immunity. Further, it is possible that in the past, when the disease was more widespread, periodic exposure to pertussis provided reinforcement of immunity throughout life; if such naturally-occurring boosters did contribute to the protection of older children and adults, low prevalence of the disease in recent years may be reflected by the appearance of a susceptible older population. Thus, the possible need to immunize adults, as well as children, may have to be considered in the future. This will require weighing the risks of widespread immunization of older children and adults against the fact that the disease in these age groups is milder than in young infants. Current data related to this question are inadequate for rational decision making.

On the other hand, the usefulness of the currently recommended booster dose at school entrance has never been fully documented. Presumably, by keeping school children free from pertussis, transmission to younger siblings in the home is prevented. Whether this final booster offers additional protection from disease and/or such transmission is unproved.

The rates of severe untoward reactions to pertussis vaccines are not defined. Furthermore, the ultimate significance, if any, in terms of permanent sequelae, of vaccine-induced somnolence, excessive screaming and high fever is unknown, and without such knowledge satisfactory recommendations for further immunization cannot be made if any of these reactions occurs. Physicians are expected to report complications of immunization to manufacturers in the United States, but compliance with this expectation is less than optimum. Many physicians are not cognizant of the importance of reporting untoward reactions or may be unaware of their clinical features. Further, both physicians and manufacturers may be held liable for damages in suits brought by patients who may suffer adverse effects from established vaccines. All these factors undoubtedly discourage reporting; without maximum reporting or some other form of surveillance, definition of the rates and significance of untoward reactions to current and future vaccines cannot be ascertained.

3. Laboratory procedures and technical requirements for the production and evaluation of pertussis vaccine exhibit certain problems that require solution.

The results of the weight-gain test in mice, used to determine toxicity of the pertussis vaccine, show variability between laboratories and therefore either the test requires more precise standardization or another method for determining toxicity is needed. This is a problem for both the test vaccine and the control reference vaccine. At present

the only test shown to have any relation to clinical reactivity in man is the mouse weight-gain test.

Section 620.4(g) for Additional Standards of Title 21, Part 600, Code of Federal Regulations states that pertussis vaccine shall have a potency of "12 units per total human immunizing dose." Certain statistical variations in estimates of actual potency that provide some assurance that the product probably does contain 12 units per total human immunizing dose are permitted based on the number of assays performed. This is in recognition of inherent variability in this type of assay. Identification and improved control of the factors influencing the variability of this test is needed.

Further, definition of the total immunizing dose in the Regulations as 12 units (3 doses of 4 units each) is now at variance with current practice and the recommendations of national advisory committees in that 4 doses of 4 units each are now advised and employed (see section on Use and Contraindications).

During the first studies of efficacy, agglutination tests were carried out by tube dilution, which required rather large amounts of sera. The microtests in general use today need to be standardized, since there is a tendency for each laboratory to use its own adaptation of the test, making comparisons among results from different laboratories almost impossible. However, agglutination antibodies may only be indirectly associated with protection, and may not constitute the protection-specific antibody. A more specific test should be substituted if and when it becomes available.

Recommendations

1. The Panel strongly recommends that adequate public support be provided for studies of the pathogenesis of pertussis and the biology of the organism, particularly as related to the immunology of pertussis, the complications of the disease, and the untoward reactions to immunization. Without such basic studies a more effective and safer pertussis vaccine cannot be developed.

2. Surveillance of pertussis in well-defined populations should be undertaken. Such surveillance would have 3 purposes: first, to determine the incidence of the disease in the United States, including distribution by age and vaccine status; second, to evaluate the possibility that a change in serotypes of Bordetella pertussis in a community causes outbreaks of pertussis in individuals previously immunized with serotypes formerly present; and, third, to determine whether the current infrequency of the disease in the United States may ultimately result in a population of older children and adults whose immunity has waned because of a lack of repeated exposure to the organism.

The Panel is convinced that currently employed surveillance systems to identify adverse reactions to pertussis vaccine are inadequate and recommends that definitive steps be taken by the appropriate subdivisions of the Public Health Service to improve them. Several alternatives are available. Perhaps the same channels as those proposed for reporting of adverse drug reactions can be utilized. Special field stations with sufficient populations under surveillance may have to be established and funded.

3. Specific recommendations of the Panel regarding the production, use, and evaluation of pertussis vaccines include the following:

The weight-gain test in mice used to determine toxicity of pertussis vaccine needs revision to include specifications regarding mouse strain(s) to be used and a reference standard. Studies should be undertaken to develop other assays predictive of human reactivity. Obviously, better definition of the organisms' biological characteristics (Recommendations, No. 1.) would facilitate prediction and prevention of reactivity in man.

The agglutination test used to determine vaccine response in humans should be standardized. It is recommended that a reference serum be used for comparison. A reference laboratory should be available at the Bureau of Biologics. The interval between immunization and obtaining serum for testing of the serologic response must be specified. An acceptable titer obtained by a standardized method should be defined; titer rises or geometric mean titers are not adequate to evaluate immunogenicity. (See discussion on Efficacy, Pertussis Generic Statement.)

Regulations concerning the maximum human dose should be updated to reflect current recommendations and practices. It should be required that pertussis vaccine have a potency of 4 protective units per single human dose. The upper estimate of a single dose should not exceed 8 protective units.

The vaccine label should warn that if shock, encephalopathic symptoms, convulsions or thrombocytopenia follow a vaccine injection,

no additional injections with pertussis antigens should be given (immunizations can be continued with DT). The label should also include a cautionary statement about fever, excessive screaming and somnolence.

Any fractionated vaccine that differs from the original whole cell vaccine should be field tested until better laboratory methods for evaluating immunogenicity in man are developed. Field testing should include agglutination testing and, if possible, evaluation of clinical efficacy in man.

4. Pertussis vaccine is one of the immunizing agents for which it is strongly urged that legislation be enacted to provide reasonable Federal compensation to the few individuals injured and disabled by participating in a meritorious public health program. Such legislation would protect manufacturers and physicians against liability in situations in which the injury was not a consequence of defective or inappropriate manufacture or administration of the vaccine.

Basis for Classification

Because field trials are not now feasible, at least in this country, the standard of efficacy upon which major reliance has to be placed is a mouse protection test, the results of which were correlated closely with the original field tests upon which evidence of efficacy for pertussis vaccine is based. Agglutination titers provide general but not absolute correlative support. Therefore, vaccines prepared in accordance with the specifications of those found effective in field trials and meeting standards for mouse protection are considered eligible for assignment to Category I especially when supported by adequate agglutination titers.

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SPECIFIC PRODUCT REVIEWS

PERTUSSIS VACCINE MANUFACTURED BY BUREAU OF LABORATORIES,

MICHIGAN DEPARTMENT OF PUBLIC HEALTH

1. Description. No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. Labeling--a. Recommended use/indications. No labeling was provided.

b. Contraindications. No labeling was provided.

3. Analysis--a. Efficacy--(1) Animal. No information was provided.

(2) Human. No information was provided.

b. Safety--(1) Animal. No information was provided.

(2) Human. No information was provided.

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

4. Critique. In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

PERTUSSIS VACCINE ADSORBED MANUFACTURED BY BUREAU OF LABORATORIES,
MICHIGAN DEPARTMENT OF PUBLIC HEALTH

1. Description. Pertussis vaccine, adsorbed is a suspension of killed Bordetella pertussis organisms in 0.85 percent saline solution mixed with a suspension of aluminum phosphate (no more than 1.5 mg per single dose), and preserved with thimerosal, 0.01 percent. The number of organisms is equal to 8 to 16 opacity units per 0.5 ml. Formaldehyde is added "if needed" to a concentration of not more than 0.01 percent. Each 0.5 ml contains 4 protective units.

2. Labeling--a. Recommended use/indications. May be used alone for active immunization if it is desired to begin after 3 months or for booster during outbreaks. Routine immunization should be carried out with DTP. Three intramuscular injections each 0.5 ml, 4 to 6 weeks apart, boosters at 2 to 5 years of age. Not recommended above the age of 5.

b. Contraindications. (1) Respiratory or other acute infections; (2) cerebral damage; (3) severe febrile reactions; (4) encephalitic reaction to vaccine; and (5) persons on corticosteroid treatment.

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

(2) Human. A study reported in The British Medical Journal, (Ref. 1) used this product. Table 1 in the study states a "plain suspension" was used, while this product is adsorbed. Vaccine used in the

study had $10,000 \times 10^6$ organisms per ml. Dosage was 1, 2, 3 ml at monthly intervals for total of $60,000 \times 10^6$ organisms. Children 6 to 18 months were immunized. Vaccine lot D 231 was tested in 630 subjects with 655 controls; vaccine lot A 236 was tested in 1,056 subjects with 993 controls. The following table is a summary of the data presented in the study.

Table 1

Vaccine	Attack rate/1,000 child months		% attack rate in home exposure		% attack rate in other exposures	
	Vac.	Univac.	Vac.	Univac.	Vac.	Univac.
D 231	0.97	7.04	7.3	79.5	4.6	36.7
A 236	0.60	6.48	8.9	90.0	3.8	34.8

Comparison of attack rates in the 2 groups indicates that the vaccine provided approximately 80 to 85 percent protection against pertussis.

b. Safety. One child in 5 was visited 24 to 72 hours after each injection. No severe local or general reactions were observed although a number developed temperature rises within 24 hours.

No specific data are provided for the present product.

c. Benefit/risk ratio. The benefit-to-risk assessment is favorable.

4. Critique. The human efficacy data would appear to prove the value of this product, but the studies were based upon a differing dosage schedule of a plain, not adsorbed, vaccine (with a greater dosage of antigen). Extrapolation of the British Medical Research Council data to the present product may not be entirely justified but provides some of the best available data.

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.

PERTUSSIS VACCINE MANUFACTURED BY DOW CHEMICAL COMPANY

1. Description. No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. Labeling--a. Recommended use/indications. No labeling was provided.

b. Contraindications. No labeling was provided.

3. Analysis--a. Efficacy--(1) Animal. No information was provided.

(2) Human. No information was provided.

b. Safety--(1) Animal. No information was provided.

(2) Human. No information was provided.

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

4. Critique. In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

PERTUSSIS VACCINE, FLUID MANUFACTURED BY ELI LILLY AND COMPANY

1. Description. Pertussis vaccine, fluid, is an unwashed suspension of killed Bordetella pertussis cells grown in modified Cohen-Wheeler medium. The methods of killing and detoxification are not given. The product is preserved with 1:10,000 merthiolate and the total human immunizing dose (1.5 ml) contains the equivalent of 12 antigenic units of the United States standard pertussis vaccine.

2. Labeling--a. Recommended use/indications. For active immunization against pertussis. The package circular recommends that three 0.5 ml doses be administered subcutaneously at intervals of three to four weeks for primary immunization. A booster or "optimum stimulating" dose of 0.25 to 0.5 ml is recommended for administration approximately one year after primary immunization.

b. Contraindications. Elective immunization should be postponed in the presence of acute infections. Postvaccinal neurologic disorders contraindicate further injections. Personal or family history of central nervous system damage or convulsions is an indication for fractional dosages. It is noted that corticosteroids may interfere with the immune response.

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

(2) Human. No specific studies on this product are presented or cited. Claims for efficacy appear to be based largely on demonstrated correlation of potency in mice and protective efficacy in children (Ref. 2).

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

(2) Human. No specific data on this product were presented. The manufacturer's submission indicated no consumer complaints over a 5-year period.

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

d. Labeling. No mention is made of the desirability of using DTP for immunization of most infants.

Although postvaccinal neurological disorders including convulsions are listed as a contraindication to further use, the labeling goes on to recommend fractional dosage. This is contradictory.

The reference to avoiding use of the vaccine when polio is present in the community is outdated and should be deleted.

4. Critique. It should be noted that this is a whole-cell pertussis vaccine, and, as such, differs significantly from that used in this manufacturer's DTP, in which a "solubilized" bacterial fraction is employed.

While no specific studies on this product are presented or cited, claims for efficacy are justifiably based largely on the demonstrated correlation of potency as determined by the intracerebral mouse protection test and protective efficacy in children.

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 recommendations of this Report.

PERTUSSIS VACCINE, FLUID MANUFACTURED BY LEDERLE LABORATORIES
DIVISION, AMERICAN CYANAMID CO.

1. Description. No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. Labeling--a. Recommended use/indications. No labeling was provided.

b. Contraindications. No labeling was provided.

3. Analysis--a. Efficacy--(1) Animal. No information was provided.

(2) Human. No information was provided.

b. Safety--(1) Animal. No information was provided.

(2) Human. No information was provided.

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

4. Critique. In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

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

1. Description. The manufacturer did not provide a description of the monovalent pertussis vaccine for which a license is maintained. Instead a submission for pertussis vaccine combined with diphtheria and tetanus toxoids is provided, and includes details of the production of the pertussis component. The manufacturer has released no monovalent pertussis vaccine for 12 or more years.

2. Labeling--a. Recommended use/indications. None is provided.

b. Contraindications. None is submitted.

3. Analysis--a. Efficacy--(1) Animal. This pertussis vaccine prepared for the combined product meets Federal requirements.

(2) Human. The evidence for efficacy in humans comprises a study from 1950 in which 75 infants were immunized with this pertussis vaccine combined with diphtheria and tetanus toxoids (Ref. 3). In this study, satisfactory pertussis immunization was achieved as determined serologically.

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

(2) Human. When employed in combination with diphtheria and tetanus toxoids no serious reaction occurred in 100 infants immunized.

c. Benefit/risk ratio. The benefit-to-risk assessment cannot be determined for this product in the monovalent form.

4. Critique. This vaccine has not been marketed for more than 12 years and no specific data related to this product in the monovalent

form were provided. Except for rare instances of community outbreaks of pertussis in which it might be desirable to administer monovalent pertussis vaccine, these products do not enjoy wide usage.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

PERTUSSIS VACCINE MANUFACTURED BY PARKE, DAVIS AND CO.

1. Description. A sterile saline suspension of centrifuged and resuspended "selected" strains of phase 1 Bordetella pertussis is grown on semi-synthetic liquid medium. The organisms are inactivated by incubation in the presence of formaldehyde. Thimerosal 0.01 percent is added as a preservative. Total dose contains 12 units of pertussis vaccine. The product is currently not marketed.

2. Labeling--a. Recommended use/indications. This product is recommended for "rapid primary immunization" of infants and children against pertussis - to be followed ordinarily by immunization with DTP in order to complete immunization against the other antigens in this combination; 3 doses of 0.5 ml each are given subcutaneously at 3 to 4 week intervals or, if rapid immunization is indicated, at 1 week intervals. However, the longer interval is probably better. A booster dose of 0.5 ml is recommended 1 year after basic immunization and at 3 to 6 years of age or in the presence of actual or potential exposure to the disease in children under 6.

b. Contraindications. Defer immunization in presence of cerebral damage, active infection, or acute respiratory disease. Discontinue if encephalopathic symptoms appear. Give smaller graduated doses if a systemic reaction occurs.

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

(2) Human. Antibody response data of 1961 to 1963, (Ref. 4) appear satisfactory, but it is not clear that this can be extrapolated to the current product.

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

(2) Human. No data on this particular product are presented. No market experience is reported.

c. Benefit/risk ratio. This cannot be judged in view of the absence of data on reactions to this particular product.

4. Critique. This is a fluid pertussis vaccine made by the pioneer firm in developing pertussis vaccine in the United States, but differing from their classical "Sauer vaccine" in that it is made in liquid medium instead of on a solid Bordet - Gengou medium. No data are provided on human safety or human antibody responses; the last package insert is dated 1966. This is an inactive product. Only illegible photostats of labels are presented. The emphasis in the package insert on using the fluid vaccine for "rapid immunization" cites no reference supporting this recommendation.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

PERTUSSIS VACCINE ADSORBED MANUFACTURED BY

PARKE, DAVIS AND CO.

1. Description. This is an aluminum phosphate adsorbed pertussis vaccine, currently not on the market. It contains 15 opacity units per 0.5 ml dose and 4 antigenic units per dose. It is centrifuged, resuspended in 0.9 percent saline, mixed with aluminum phosphate and 0.01 percent thimerosal is added.

2. Labeling--a. Recommended use/indications. This vaccine is recommended as an efficient method of immunizing infants and children against whooping cough when a monovalent immunizing agent is indicated; these circumstances are no further defined. Recommendations for routine immunization are standard.

b. Contraindications. The usual contraindications are noted, particularly with regard to children having any history or signs of encephalopathy.

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

(2) Human. Evidence of direct human efficacy is not presented.

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

(2) Human. Data are reported in the submission (Ref. 4) concerning 27 children who received the adsorbed pertussis vaccine in 1967, of whom 5 had systemic reactions as measured by fever. No other information regarding human safety is included.

c. Benefit/risk ratio. The data provided are inadequate to make a determination.

4. Critique. This is an aluminum phosphate adsorbed pertussis vaccine, currently not on the market, but one that would meet current standards for animal safety. Whether it is efficacious and safe in humans is not possible to determine from the data submitted.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

PERTUSSIS VACCINE MANUFACTURED BY TEXAS DEPARTMENT
OF HEALTH RESOURCES

1. Description. This product is prepared from Phase I strains of Bordetella pertussis and is an unwashed suspension of the organisms in physiological sodium chloride solution, killed and preserved by thimerosal in final concentration of 1:10,000.

The vaccine is tested for antigenic potency by the mouse-protection test and the degree of protection must equal or exceed that of the United States standard pertussis vaccine. The total immunizing dose contains 12 units.

2. Labeling--a. Recommended use/indications. This preparation is recommended for active immunization of children. Three doses of 1.0 ml of the vaccine are given deep subcutaneously at 3 to 4 week intervals. The labeling also recommends that booster doses of 0.3 or 1.0 ml be given at about 2 years of age, again at the age of 5 or 6 years, during epidemics and after known exposure to the disease. Pertussis vaccine plain is not recommended for immunization of children under 6 months of age. "In this group, the pertussis vaccine with the mineral adjuvant is the material of choice."

b. Contraindications. These include any respiratory or other acute infections. The presence of cerebral damage in an infant is an indication for delay in immunizations. It is advised that in such children and in those experiencing severe febrile reactions with or without convulsions, immunization procedures should be delayed and/or

given in fractional doses. This is partly incorrect, and the label should state that in children who experience shock, convulsions, encephalopathy, excessive screaming or thrombocytopenia, after vaccinations with a pertussis vaccine, no further injections of any pertussis vaccine should be given.

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

(2) Human. No data are provided relative to this particular product, but reference is made to the general data accumulated in the United States, including a chart of decreasing incidence of pertussis in Texas over time (Ref. 5).

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

(2) Human. This product has been produced since 1945. The number of released doses is not given, but it is stated that there is a lack of reaction reports to the single fluid antigen in Texas.

c. Benefit/risk ratio. The benefit-to-risk assessment appears to be satisfactory but is not well documented.

d. Labeling. There are two flaws in the label as described above:

(i) The lack of a clear statement that DPT is usually the vaccine of choice for routine immunization of children.

(ii) No mention of convulsions, shock, encephalopathy, excessive screaming or thrombocytopenia following a dose of pertussis vaccine (plain or combined) as an absolute contraindication for further immunization of pertussis (but immunization can usually be continued with DT).

5. Critique. It is not known how many doses of this product have been distributed. The immunizing dose is 1 ml instead of 1/2 ml which is unusual. The labeling is partly misleading as described above.

6. Recommendations. The Panel recommends that this product be placed in Category I 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.

PERTUSSIS VACCINE MANUFACTURED BY WYETH LABORATORIES, INC.

1. Description. No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. Labeling--a. Recommended use/indications. No labeling was provided.

b. Contraindications. No labeling was provided.

3. Analysis--a. Efficacy--(1) Animal. No information was provided.

(2) Human. No information was provided.

b. Safety--(1) Animal. No information was provided.

(2) Human. No information was provided.

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

4. Critique. In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must recommend revocation of licensure for administrative reasons.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

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(1) Bedson, S. P., W. C. Cockburn, et al.,
"Prevention of Whooping Cough by Vaccination by a
Medical-Research Council 'Investigation,'" The British
Medical Journal, 1:1463-1471, 1951.

(2) BER VOLUME 2046.

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(4) BER VOLUME 2005.

(5) BER VOLUME 2101.

GENERIC STATEMENT

Diphtheria and Tetanus Toxoids and Pertussis Vaccine (DTP)

See Generic Statement for Monovalent Components

Description

This product is a combination of diphtheria and tetanus toxoids with pertussis vaccine, intended for the primary immunization and maintenance of immunity against diphtheria, tetanus and pertussis in children 6 years of age or less.

Production

DTP comprises diphtheria and tetanus toxoids and pertussis vaccine prepared in a manner usually similar to that of the monovalent preparations, and combined into a single preparation. Both fluid and adsorbed products are currently licensed and used in the United States. One manufacturer produces a partially purified fraction of pertussis organisms.

Use and Contraindications

DTP is recommended for the primary immunization of infants and children 6 years of age or younger. Recommended schedules are provided by the Advisory Committee on Immunization Practices of the United States Public Health Service, the American Academy of Pediatrics, and the American Public Health Association.* Primary immunization comprises a series of 4 doses administered subcutaneously or intramuscularly and the adsorbed preparations should be given intramuscularly.

*These 3 organizations are referred to as National Advisory Committees in other Generic Statements of this Report.

The Advisory Committee on Immunization Practices recommends that the first 3 doses be given at 4 to 6 week intervals with a fourth dose approximately 1 year after the third injection. Ideally, immunization should begin at 2 to 3 months of age or at the time of a 6 week check-up if that is more practical. It is advisable not to administer DTP to individuals 7 years of age or older because untoward reactions to the pertussis component may be severe.

Contraindications are of 2 general types. The first of these is a severe hypersensitivity response to a prior injection. The other is a definite or suspected untoward reaction to the pertussis component of DTP. (See Generic Statement for Pertussis Vaccine.)

As with the individual components, the administration of DTP should be deferred in the presence of a febrile illness, because of possible confusion as to the etiology of persistent fever. Individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time.

Safety

There is no evidence that the combination of tetanus and diphtheria toxoids with pertussis vaccine synergistically increases the likelihood of adverse reactions over that observed with the individual components.

The toxoid components are tested for detoxification and the final product must be tested for safety according to Federal requirements.

Efficacy

Laboratory and animal procedures for determining the potency of DTP, as specified by Federal requirements, are carried out. In the case of the pertussis component of DTP the mouse protection test affords a reasonably satisfactory means of correlating an animal model with protection in humans (See Generic Statements for Monovalent Products). An immunologic advantage of DTP over the monovalent toxoids is that the pertussis component exerts some adjuvant effect on diphtheria and tetanus toxoids.

Special Problems

1. The available information indicates that the components of DTP, singly or in combination, are more immunogenic in the adsorbed preparations than in the fluid products. It is therefore questioned by some whether continued production and use of fluid toxoids and vaccines have any advantage.

2. DTP has been one of the most widely used vaccines. Most experiences therefore with adverse reactions to the components have been derived from experience with the combined product rather than from the monovalent preparations. Problems with the individual components are similar to those of the monovalent products and may be summarized as follows. (See Generic Statements for Monovalent Diphtheria and Tetanus Toxoids and Pertussis Vaccine for detailed discussion.)

a. Diphtheria. Diphtheria toxoid, fluid or adsorbed, single or in combination, even with the adjuvant effect of pertussis vaccine, is

not as effective an immunizing agent as might be desired. Evidence for this includes the occasional occurrence of diphtheria in immunized individuals and infections with nontoxigenic strains. Furthermore, there is concern about the permanence of immunity and the effectiveness of the present booster program in the light of the decreased frequency of exposure to the organism in the community, a phenomenon that may have provided repeated natural enhancement of immunity in the past. Whether increased purification of the toxoid may reduce immunogenicity is also unknown. Other problems with the diphtheria component include non-specific reactivity and the lack of an animal model that would obviate field testing of improved toxoids in humans.

b. Tetanus. There is evidence that recent changes in manufacturing procedures, designed to reduce reactivity, may have lowered the immunizing potency of current tetanus toxoids compared to those in use 30 years ago.

c. Pertussis. Because the pathogenesis of pertussis and the biology of Bordetella pertussis are poorly understood, knowledge of the immune response and the pathophysiology of both the disease and immunization is limited. Without better definition of the components of the organism and their relation to disease and immunity, attempts to improve immunogenicity and reduce reactivity of pertussis vaccines are seriously hampered. Additional unknown facts about pertussis and pertussis immunization that require study include the true incidence of the disease, whether present vaccines need to reflect currently prevalent strains of

Bordetella pertussis, the permanence of vaccine-induced immunity, and the true frequency and significance of the various untoward reactions. Furthermore, laboratory testing procedures, used in the production and evaluation of pertussis vaccines, require improvement and standardization.

Recommendations

Recommendations regarding DTP are the same as those in the generic statements for the monovalent components of this product. They may be summarized as follows:

1. Diphtheria--a. Upgrading of surveillance of the diphtheria-immune status of the population is recommended in order to anticipate the possible development of a susceptible population in the future.

b. Efforts should be made to develop an animal model or other laboratory technique for evaluating antigenicity that correlates well with immunogenicity in humans.

c. Public support for the development of a better immunizing agent against diphtheria should be provided. Worthy objectives include not only more immunogenicity but also less reactivity.

2. Tetanus--a. Continued efforts should be made to establish, for routine lot-to-lot control, the usefulness of the quantitative technique of the evaluation of tetanus toxoids against the International Standards. This technique is required by the European Pharmacopoeia.

b. Because some current tetanus toxoids appear to have somewhat less antigenic potency than those employed in the past, monitoring of the immune status of a human population sample should be conducted over years in order to ascertain the necessity for continuing booster doses.

3. Pertussis--a. Adequate public support should be provided for studies of the pathogenesis of pertussis and the biology of the organism, particularly as related to the immunology of pertussis, the complications of the disease, and the untoward reactions to immunization. The purpose of such studies would be to develop a more effective and safer vaccine.

b. Enhanced surveillance of pertussis and the complications of pertussis immunization is strongly recommended.

c. Certain procedures concerning the production and evaluation of pertussis vaccine need to be reevaluated for improvement in precision. These include the mouse weight-gain test, the agglutination test in man, the maximum allowable potency of the human dose, and the inclusion of a clearcut warning on the package label about untoward reactions.

d. Until better laboratory methods for correlating animal models with immunogenicity in man are developed, fractionated vaccines must be tested in field trials as they are developed.

e. Legislation should be enacted that provides public authorization for recompense to individuals who incur rare, but unpredictable and unpreventable, serious reactions to vaccines, including pertussis vaccines.

Basis for Classification

The basis for classification of this combined vaccine is the same as that used for the individual components. Since DTP is universally

recommended for primary immunization of infants and children, assurance of efficacy is especially germane, and is reasonably obtainable. Serologic evidence of efficacy for the DT components is therefore considered necessary, despite the acknowledged adjuvant effect of pertussis.

BIBLIOGRAPHY

- (1) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," Morbidity and Mortality Weekly Report, Suppl. 21(25):4-5, June 24, 1972.
- (2) "Diphtheria - Tetanus - Pertussis," In: Center for Disease Control, United States Immunization Survey: 1975, Health, Education, and Welfare Publication No. (Center for Disease Control), 76-8221:25-30, 1977.
- (3) Center for Disease Control, "Reported Morbidity and Mortality in the United States 1976," Morbidity and Mortality Weekly Report, Suppl., Health, Education, and Welfare Publication No. (Center for Disease Control), 77-8241:August 1977.
- (4) VACCINUM TETANICUM ADSORBATUM, supplement to Volume III, pp. 174-178, European Pharmacopoeia 1977, Maisonneuve, S.A., 57 Saint Ruffine, FRANCE.

SPECIFIC PRODUCT REVIEWS

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED MANUFACTURED
BY BUREAU OF LABORATORIES, MICHIGAN DEPARTMENT OF PUBLIC HEALTH

1. Description. Contains "purified" diphtheria (10 to 20 Lf per 0.5 ml) and tetanus toxoids (5 to 10 Lf per 0.5 ml), aluminum phosphate adsorbed, combined with a suspension of Bordetella pertussis organisms (8 to 16 opacity units per 0.5 ml). After combination, the potency of each component meets or exceeds Federal requirements. The amount of aluminum phosphate will not exceed 2.5 mg per single human dose (0.5 ml). The product is preserved with 0.01 percent thimerosal. The concentration of formaldehyde may not be greater than 0.01 percent.

2. Labeling--a. Recommended use/indications. Used in children 5 years of age and younger for basic immunization, periodic reinforcing or booster doses, 0.5 ml intramuscularly at 2 to 3 months of age, 3 injections given 4 to 6 weeks apart followed by reinforcing dose 6 to 12 months later and booster prior to entering school.

b. Contraindications. Contraindications include acute respiratory infections and corticosteroid or immunosuppressive therapy. If an encephalitic reaction occurs, further immunization should be carried out with DT adsorbed.

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

(2) Human. Data are provided (Ref. 1) to demonstrate immunogenicity when a product which included equivalent amounts of diphtheria

and tetanus toxoids and pertussis vaccine but also poliomyelitis vaccine and which had phemerol (benzethonium chloride) rather than thimerosal as a preservative was used in primary immunization. Thirty-eight children age 4 to 6 months, and 39 children, age 7 to 12 months were immunized and bled prior to immunization and 2 weeks after the third injection. Diphtheria and tetanus antitoxin titers and pertussis agglutination titers were satisfactory in all children, as measured in the post-immunization serum. Booster responses were studied in 290 who received 0.2 ml of DTP 13 years after primary immunization; antibody levels were determined at 1, 2 weeks, 2, 6, 12 and 24 months. The responses to tetanus and diphtheria were satisfactory in all. Those who failed to show a 4-fold or greater increase in antitoxin titers had prebooster levels of >0.01 u per ml. The vaccine used contained less pertussis antigen than recommended, and 25 of 138 (of whom 24 had initial titers of <80) failed to show a 4-fold increase in pertussis agglutinin titer.

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

(2) Human. When 0.2 ml of DTP was administered to older persons, including adults, (305 subjects) local reactions were severe (46 percent), moderate (30 percent), mild (22 percent) and none in only 2 percent. Severe reactions were associated with mild systemic reactions. Reactogenicity in children is not defined in the submission.

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

4. Critique. The data on immunogenicity appear satisfactory although the actual immunogen utilized included poliomyelitis vaccine and a different preservative.

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 TOXOID AND PERTUSSIS VACCINE ADSORBED MANUFACTURED
BY DOW CHEMICAL COMPANY

1. Description. No data have been provided by the manufacturer for this product for which they are presently licensed.

2. Labeling--a. Recommended use/indications. No labeling was provided.

b. Contraindications. No labeling was provided.

3. Analysis--a. Efficacy--(1) Animal. No information was provided.

(2) Human. No information was provided.

b. Safety--(1) Animal. No information was provided.

(2) Human. No information was provided.

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

4. Critique. In the absence of any data from the manufacturer regarding this specific product, and in the absence of any labeling for this product, the Panel must necessarily recommend revocation of this license.

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 and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED

MANUFACTURED BY DOW CHEMICAL COMPANY

1. Description. There are 2 diphtheria and tetanus toxoids and pertussis vaccine, adsorbed, products which differ only in the technique of adsorption. Both represent combinations of toxoids prepared from organisms grown in Mueller-type media, Bordetella pertussis grown on solid charcoal agar medium without blood substances. The toxins are detoxified with formaldehyde and concentrated by alcohol fractionation (Pillemer method). Each dose (0.5 ml) contains 10 Lf diphtheria toxoid, 5.33 Lf tetanus toxoid and 15 opacity units of pertussis vaccine. The preservative is 1:10,000 thimerosal.

The pertussis component includes 4 strains of Bordetella pertussis which are bulk standardized at 90 opacity units.

The refined toxoids are adsorbed on either aluminum phosphate (0.23 mg aluminum) or potassium alum (0.14 mg aluminum).

2. Labeling--a. Recommended use/indications. The package circular recommends these preparations for routine immunization of infants and children, 8 weeks to 6 years of age, against diphtheria, pertussis and tetanus. Three 0.5 cc intramuscular injections at intervals of 4 to 6 weeks are recommended for primary immunization with a reinforcing injection about 12 months after the third dose. A booster dose of 0.5 cc is recommended at 4 to 6 years of age.

b. Contraindications. Convulsions following an earlier injection contraindicates further administration of vaccines containing pertussis.

The product is not recommended for use in children over 6 years of age. The label recommends deferral of elective injections in the following situations; acute respiratory disease, or other active infection, during treatment with immunosuppressive agents, outbreaks of poliomyelitis in the community. Fractional doses are recommended in infants with cerebral injury, asthma, a strong family history of allergy, somnolence or fever of greater than 102° F with an earlier dose.

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

(2) Human. A review of the literature did not reveal any studies which included a Dow (Pitman-Moore) DTP in a trial of prophylactic efficacy.

Immunogenicity to each component is reported. With regards to the pertussis component Bordt reports (Ref. 2):

Age group	No. subjects	No. with titer <1:4 prevaccine	% conversion† <1:4 to >1:32 (0.1 ml)
<6 months	20	19	74
6 mos. - 2 yrs.	38	35	94
2 yrs. - 6 yrs.	37	32	94

The question as to whether 74 percent conversion in infants less than 6 months of age is adequate cannot be answered from the available data.

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

(2) Human. In the report by Conner and Speers (Ref. 3) 220 injections were given to children aged 2 months to 5 years and reactions followed. Two whole cell DTP vaccines were used; 1 was this product. The proportion of children who received this product is not stated. Reactions were observed in 43.6 percent of recipients; none were encephalopathic, and no febrile convulsions were seen. Local reactions (inflammation or nodule formation at injection site in 29.6 percent) and systemic reactions (30.9 percent) occurred frequently.

4. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory for the aluminum phosphate product, would be satisfactory for the potassium alum product if it is shown to be effective for primary immunization, and is satisfactory for the potassium alum product when used for booster immunization.

5. Critique. Inasmuch as there are 2 products in terms of the "adsorbant" component, the Panel considered each independently although both carry the same brand name.

The submission and supporting data provide satisfactory evidence of safety and immunogenicity for the aluminum phosphate product when used for primary immunization of infants and children.

In contrast, data were not submitted or available to provide satisfactory evidence for the immunogenicity of the potassium alum preparation.

6. Recommendations. The Panel recommends that this product, when prepared with aluminum phosphate, be placed in Category I 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, when prepared with potassium alum, 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 as the recommendations of this Report.

The Panel recommends that this product, when prepared with potassium alum, 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 the 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 ELI LILLY AND COMPANY

1. Description. This product is an alum-precipitated preparation of purified diphtheria and tetanus toxoids (Pillemer method) and extracted pertussis antigen. Each total human dose (1.5 ml) contains 15 Lf tetanus toxoid; 50 Lf diphtheria toxoid and 12 protective units of pertussis antigen. The preservative is 1:10,000 merthiolate.

The methods of preparing the toxoids are classical, but the method for preparing the extracted pertussis antigen is not given. It is stated that the procedure permits cellular debris to be discarded.

2. Labeling--a. Recommended use/indications. For simultaneous active immunization of children not over 6 years of age against diphtheria, tetanus and pertussis.

b. Contraindications. Use in the presence of acute infections should be postponed. Personal or family history of central nervous system damage or convulsions is an indication to use fractional dosage of individual antigens or 1/10 the recommended dosage of DTP.

Postvaccinal neurologic disorders, such as convulsions or encephalopathy are a contraindication to further use of pertussis antigen (note apparent contradiction to above recommendation on fractional doses). It is noted that corticosteroid may interfere with the immune response.

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

(2) Human. This particular product has never been subjected to a controlled clinical trial of its prophylactic efficacy. This is of particular concern because of the unique nature of the pertussis component. It does meet the requirements of the mouse potency test which has been correlated with human efficacy for whole-cell vaccines and Pillemer's purified pertussis antigen in the British Medical Research Council Field Trials. The product has been shown to stimulate mouse protective antibodies (measured by incubating serum with organisms, then injecting intracerebrally in mice), and agglutinating antibodies measured by a slide test (apparently not quantitated). The significance of the latter tests is unknown. (See Weihl (Ref. 4).) The toxoid components appeared to produce an adequate response.

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

(2) Human. Two studies (Refs. 3 and 4) purports to show that this vaccine produced a lower incidence of local and systemic reactions than whole-cell vaccine. It is not clear if a single lot of "Extracted" DTP was employed and how many (and which manufacturer's) whole-cell DTP vaccines were involved in the comparison. This study may be a melange of the experience of the investigators who carried out separate evaluations (C. Weihl, H. D. Riley and J. Lapin.)

This is an extensively used product. Data from manufacturer's complaint files do not indicate an excessive number of complaints or the existence of a serious problem.

c. Benefit/risk ratio. Assuming that the vaccine is efficacious, the benefit-to-risk assessment would be satisfactory, but there is insufficient information to determine this for primary immunization. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

d. Labeling. Although postvaccinal neurological disorders including convulsions are listed as contraindications to further use of the vaccine, the labeling goes on to recommend fractional dosage. This is contradictory.

The reference to avoiding the use of the vaccine when polio is present in the community is outdated and should be deleted.

4. Critique. This is the only vaccine considered by the Panel which is not a whole-cell vaccine or differs substantially from the pertussis vaccines used in the British Medical Research Council Field Trials which established the correlation of vaccine efficacy with potency assayed by the intracerebral mouse protection test. This particular type of fractionated pertussis antigen has never been subjected to a controlled field trial of prophylactic efficacy. In view of its widespread usage, this is a matter of some concern, especially since the feasibility of performing such a trial is extremely remote. While the mouse protection test provides a reasonable interim basis for assuming that the vaccine is likely to be efficacious, additional studies to provide a quantitative assessment of the agglutinin response are indicated to provide further assurance. This is especially indicated by the

uniqueness of this product and the reasonably good relationship of agglutinin titers and vaccine efficacy established in the British Medical Research Council Field Trials. Unfortunately, data on agglutinin response furnished by the manufacturer are of a qualitative nature based on a rapid slide agglutination test.

In the matter of safety, the data gives the general impression that the vaccine containing extracted pertussis antigen is somewhat less reactive than whole-cell pertussis vaccine in terms of local and minor systemic reactions. There is not sufficient basis to assume that this vaccine is any more or less safe than whole-cell vaccines in terms of the very low risk of serious encephalopathic reactions which accompanies the use of pertussis vaccines.

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.

Although meeting mouse protection test requirements this particular type of fractionated vaccine has never been subjected to a controlled field trial of prophylactic effectiveness. Such field trials do not appear to be feasible in the near future because of the relative rarity of the disease and for other practical reasons previously discussed in this report. Serological data from agglutination tests, although indicative of an immune response, are not considered definitive evidence of

protection. These factors led to a divided vote by the Panel. Therefore the Panel, by a split vote of three to two, recommends that this product be placed in Category I for primary immunization.

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 preceding 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.