Addendum to Summary For Basis of Approval: Pneumococcal Vaccine, Polyvalent (Ref. No. 82-253)

During a review of the Summary for Basis of Approval (SBA) of Pneumococcal Vaccine Polyvalent, manufactured by Merck Sharp and Dohme, it was noted that an incorrect percentage is shown in the SBA for the number of vaccine recipients who had local reactions. In item V.C. it is stated that adverse reactions such as local swelling, pain or erythema occur in approximately 5-25% of vaccine recipients.

In the package enclosure for Pneumovax 23, the manufacturer states that 21 of 29 adults (71%) had local reactions characterized principally by local soreness and induration at the injection site within 2 days after vaccination with 25 µg of a 22-valent product. The submission regarding the 22-valent product information in the license application shows the following % of subjects with local reactions: Day 0 (58.6%); Day 1 (62.1%); and Day 2 (37.9%). An additional 25 subjects received 25 µg of the 23-valent vaccine. The submission in the license application for this product shows the following % of subjects with local reactions: Day 0 (68%); Day 1 (72%); and Day 2 (32%).

M. Carolyn Hardegree, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date June 30, 1983

From Bacterial Polysaccharides Branch, DBP HFN-858

Subject Summary for Basis of Approval

To Donald Hill 7/1/83
Director, Licensing Branch - HFN-825
THROUGH: Dr. Carolyn Hardegree, Acting Director, DBP - HFN-850 mch

Reference Number: 82-253 Product License Name: Pneumococcal Vaccine, Polyvalent

Manufacturer: Merck Sharp & Dohme License #2 Product Trade Name: PNEUMOVAX-23

Merck Sharp & Dohme was licensed for Pneumococcal Vaccine, Polyvalent (14 types) in 1977. Since that time it has become apparent that additional types of pneumococci are important for worldwide disease prevention. Reference No. 1 summarizes the information leading to a reformulation of pneumococcal vaccines.

The manufacturers of pneumococcal vaccine were advised of the recommended changes in the formulation. In addition to the number of types of polysaccharides to be included, there has been a reduction in the amount of each type of polysaccharide from 50 µg to 25 µg.

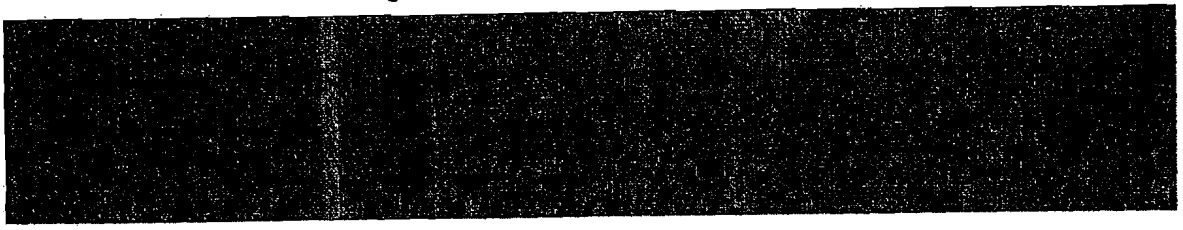
Phagocytosis of pneumococci through opsonization by specific anticapsular polysaccharide antibodies appears to be a major protective mechanism against pneumococcal infection. Type-specific antibodies appear to correlate with the opsonizing activity and vaccine efficacy.

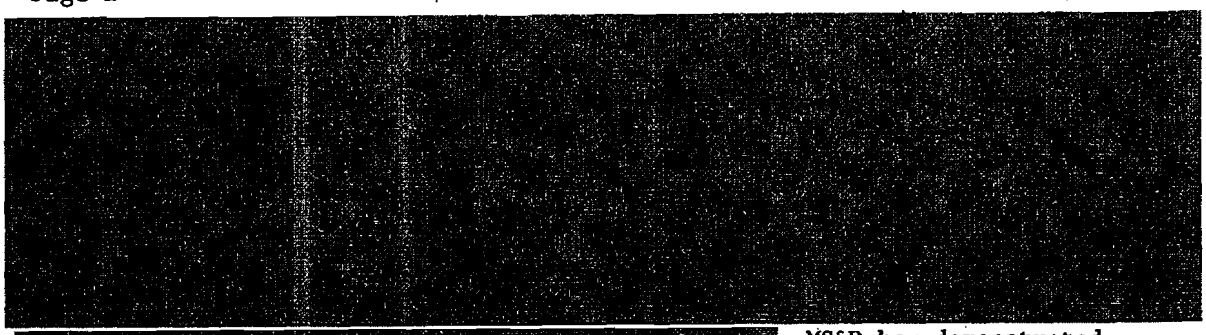
I. Indications for use: For immunization against pneumococcal disease caused by those pneumococcal types included in the vaccine in selected populations of individuals older than two years of age.

II. Dosage form and route of administration: Each 0.5 ml dose of vaccine contains 25 µg of each polysaccharide type dissolved in isotonic saline solution containing 0.25% phenol as preservative. The vaccine is packaged in a 5 dose vial, and 5 single dose vials, for subcutaneous or intramuscular injection.

III. Manufacturing and Controls:

A. Manufacturing and control tests.





MS&D has demonstrated consistency of production for the 23 types of pneumococcal capsular polysaccharides included in the vaccine.

B. Immunogenicity Studies.

Clinical immunogenicity studies were performed using a 22-valent vaccine formulated at either 50 µg/type/dose or at 25 µg/type/dose. Two groups of adult volunteers, ages 21-64 were used for the study. Twenty-three adults received 0.5 ml of the 50 µg/type dose, and 29 adults received 0.5 ml of the 25 µg/type dose. Serum samples were obtained immediately before vaccination and approximately three weeks later. Antibody responses to pneumococcal polysaccharide types were determined in the serum samples after the individuals with high pre-immunization titers (greater than of post-vaccination geometric mean titer) were removed from the analysis. The vaccine containing 50 µg/type/dose induced at least 2-fold rise of specific antibody levels in 100% of recipients, whereas the vaccine containing 25 µg/type/dose induced at least 2-fold rise of antibodies in 87-100% recipients. The immune response to the 25 µg dose was essentially the same as that seen with the 50 µg dose.

The antibody response to the type 33F polysaccharide was determined separately after it had been determined that type 33F should be added by using the 23-valent vaccine at 25 µg/type/dose. Twenty-five adult volunteers, ages 22-29, received a single 0.5 ml injection of the 23-valent vaccine. The vaccine induced at least a 2-fold rise of type 33F antibody level in 88% of recipients. The vaccine also induced at least a 2-fold rise of type 3, 6B and 19F antibodies in 88-92% of recipients.

C. Stability studies: This manufacturer's and other similar 14-valent vaccines have been shown to retain immunogenic activity in volunteers (potency) after two years of storage at 2-8°C. The individual polysaccharides of pneumococcal 22-valent vaccine (MS&D, lot 907) have maintained their molecular sizing characteristics after storage at 2-8°C for 8 months. The stability of type 33F polysaccharide was tested in a 23-valent vaccine (lot 12532/C-1380), and found to be stable when stored at 4°, These stability studies are still continuing.

Merck and the Office of Biologics are continuing their studies of stability to identify more precisely the rate of degradation of the individual pneumococcal capsular polysaccharide types

+ Types 6A and 25F have been removed from the 23-valent vaccine.

with respect to time and other storage conditions. The dating period of the 23-valent vaccine shall be 24 months, at a storage temperature of 2-8°C.

D. Methods of validation: The mechanism by which the vaccine exerts its protective effect is considered to be by induction of serum antibodies. The ability of various polyvalent pneumococcal vaccines to induce antibodies and/or to prevent disease in clinical field trials has been related to the aforementioned assays of composition, purity and potency. The exact level of antibody which can be correlated with protection is unknown.

E. Labeling: The package insert for Pneumovax-23, has been reviewed by the Office of Biologics. Merck has accepted the changes in the package insert proposed by the Office of Biologics. The package insert complies with the require-ments for format and content (21 CFR §201.57). The package and container labels conform to the requirements for labeling of biological products (21 CFR, Part 600-Subpart C).

F. Establishment Inspection: The prelicense inspection of the West Point, PA facility for the manufacture of Pneumococcal Vaccine, Polyvalent (14 types) was performed on August 17, 1977. Subsequent annual inspections of the West Point, PA facilities for pneumococcal vaccine manufacturing have revealed no significant deviations from existing regulations and licensing requirements.

G. Environmental Impact Analysis Report: Since this license amendment is for including additional types of pneumococci to an existing licensed vaccine with no other major changes in manufacturing methods, the new formulated vaccines are not considered to have a deleterious environmental impact. Therefore, it will not be necessary for the manufacturer to file a further EIAR for approval of this amendment.

H. The manufacturer has submitted in support of the application at least 3 lots each of new types of pneumococcal polysaccharide [redacted] (types 5, 6B, 9V, 10A, 11A, 15B, 17F, 19A, 20, 22F and 33F. See attached sheet, chemical analyses); seven lots of final containers (#12197, 12198, 12199, 12321, 12322, 12323, 12535); 2 lots of 22-valent (#906/CH485, 50 µg/ dose; #907/CH486, 25 µg/dose) and 1 lot of 23-valent (#79790/12535/CJ383, 25 µg/dose) vaccine for clinical immunogenicity and evaluation of adverse reactivity, 2 lots of 22-valent (#906 and 907) and 1 lot of 23-valent (12532/CJ 380) vaccine for stability study; 6 lots of 23-valent (81660/14559, 14659/14558 for release once the license amendment is approved. 12535, 14560, 14561, 14663)

I. [redacted]

IV. Pharmacology.

The vaccine is composed of 23 chemically and serologically distinct capsular polysaccharides of Streptococcus pneumoniae (pneumococci). These capsular polysaccharides are immunogenic and induce serum antibodies and thereby are expected to confer type-specific disease immunity against pneumococcal disease.

V. Medical

A. Pneumococci cause serious disease in individuals of all ages. The attack rate of pneumococcal disease increases in individuals over 50 years of age. Individuals who have had their spleen removed or have malfunction-ing spleen, as seen in excessive hemolytic states such as sickle cell anemia, are particularly at risk to severe and overwhelming pneumococcal disease. Despite antimicrobial therapy, approximately 5-10% of individuals who have pneumococcal pneumonia and/or bacteremia succumb to their disease. In addition, antimicrobial therapy and other supportive measures still have not reduced the morbidity and mortality of pneumococcal meningitis below 50%. Further, there are now appearing, with increasing regularity, pneumococcal strains with decreased sensitivity to penicillin and acquired resistance to many other antibiotics. Thus, prevention of this disease is worthwhile.

B. Clinical studies of MS&D as well as those of other licensed manufacturers have been reported regarding immunogenicity and vaccine efficacy. Formulation of the polysaccharide types into a polyvalent mixture does not inhibit the antibody response to the individual polysaccharides. The antibody response has been shown to be correlated with protection and greater than 2-fold rise of antibodies can be induced in 87-100% of vaccine recipients.

C. Adverse reactions such as local swelling, pain or erythema, occur in approximately 5-25% of vaccine recipients. These reactions are considered minor and do not interfere with the benefit/risk provided by this vaccine for the patient. Low grade fever (less than 100.9°F) occurs occasionally and is usually confined to the 24-hr period following vaccination. Although rare, fever over 102°F has been reported. Reactions of greater severity, duration, or extent are unusual. Anaphylactoid reactions have rarely been reported. Incidences of adverse reactions have been reported among adults receiving revaccination with pneumococcal vaccine.

The new drug labeling is considered informative, accurate, and consistent with the latest published scientific information.

VI. Approved Package Insert - A draft copy of the approved package insert is attached to this report.

Carl E. Frasch, Ph.D. Joan C. May, Ph.D. H. Donald Hochstein, Ph.D.

Chi-Jen Lee, Sc.D.
Chairperson

Reference 1. Robbins, J.B., Austrian, R., Lee, C.J., Rastogi, S.C., Schiffman, G., Henrichsen, J., Makela, P. H., Broome, C.V., Facklam, R.R., Tiesjema, R.H., and Parke, Jr., J.C. Considerations for formulating the second generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. J. Infec. Dis. 1983 (In press).

Attachment