3.

A CASE STUDY: EVALUATING THE SAFETY AND EFFICACY OF PNEUMOCOCCAL VACCINE

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Obviously one can always do more and more clinical studies and, with each well done study, advance our knowledge. Even today we are still learning new things about vaccines licensed decades ago.

It is important, however, for the judgment to be made at some point that the product is ready for licensure and to weigh the benefits of delay in gaining new data against the risks to those who are deprived by this delay in being immunized and protected.

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Deputy Director, Bureau of Biologics
May 23, 1979

BACKGROUND AND INTRODUCTION

Investigators since the 1800's have attempted to evaluate the safety and efficacy of medical technologies and procedures (U.S. Cong., OTA, September 1978). Efforts during the first half of the 19th century were generally unsophisticated and tended to focus on safety, however, and many medical therapies at the time were not efficacious. When the ineffectiveness of many technologies was demonstrated through the application of controlled trials and statistical techniques during the latter half of the 19th century, the public's confidence in medicine sharply declined.

The concepts of safety and efficacy as applied to medical technologies and procedures have generated considerable public debate. While most people would agree that medical technologies and procedures should be safe and efficacious, there is little consensus on the types of criteria and methods that should be used to evaluate safety and efficacy.

Federal authority to regulate the quality of vaccines produced in the private sector dates from 1902, the year Congress enacted the first biologics control act. This act, the Virus Serums and Toxins Act of 1902, and pursuant regulations issued in 1903, 1909, and 1919, were incorporated into section 351 of the Public Health Service Act of 1944 and remain in force today, Current Federal authority to regulate vaccine safety and efficacy also is based on the 1962 amendments to the Food, Drug, and Cosmetic Act of 1938. Investigational new drug (IND) regulations developed from the 1962 amendments have been applied to biologics since 1963. (See appendix 3.1.)

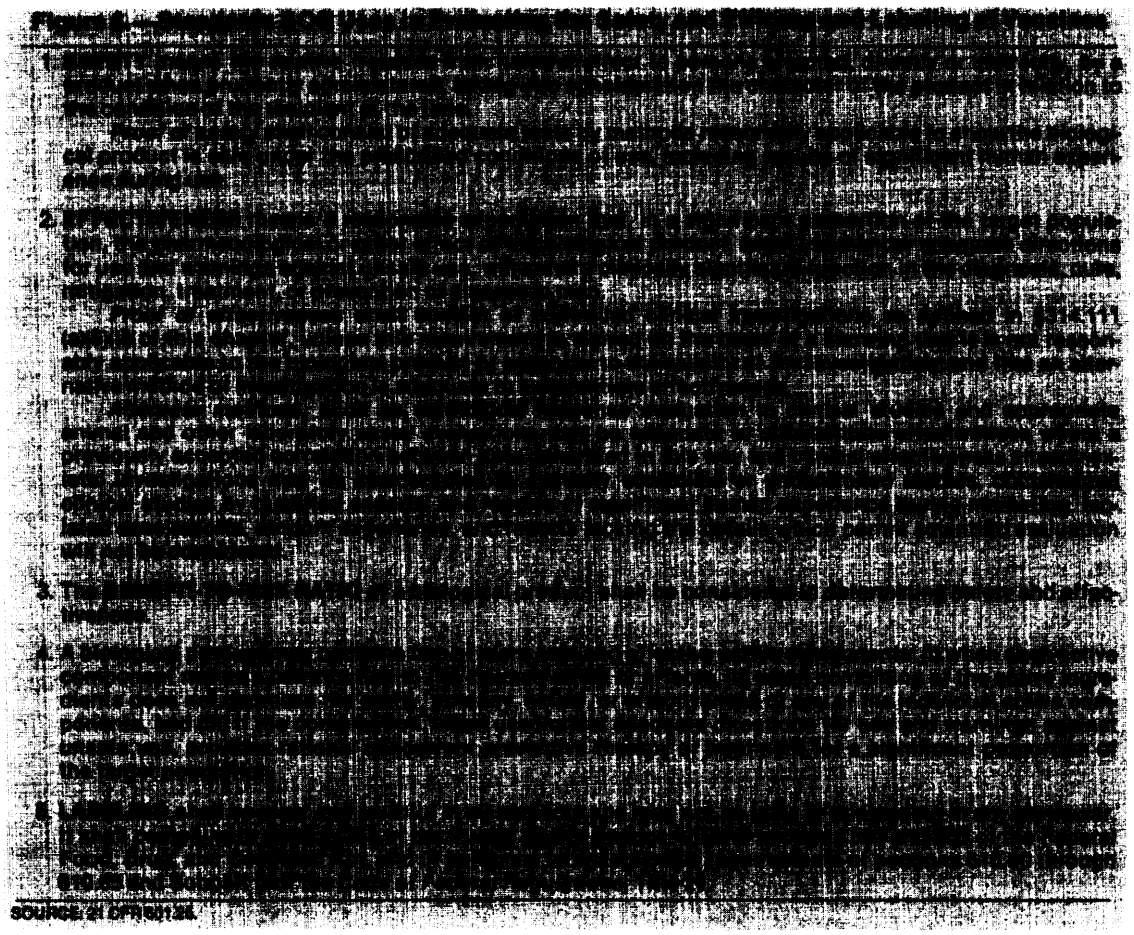
Many regulations that establish the standards and procedures that the Food and Drug Administration (FDA) uses to evaluate the safety and efficacy of investigational, as well as marketed, vaccine products were promulgated in 1972. In that year, responsibility for helping to ensure the safety and efficacy of biological products was transferred to FDA from the National Institutes of Health (NIH), which had had this responsibility for over 20 years.

The general standards that FDA's Bureau of Biologics (BOB) uses to evaluate the safety and efficacy of vaccines and other biological products are shown in figure 6. As noted in OTA's report *Assessing the Efficacy* and Safety of *Medical Technologies,* definitions of efficacy and effectiveness vary substantially, and often these terms are used interchangeably. In that OTA report, the two were differentiated as follows (U.S. Cong., OTA, September 1978):

Efficacy: The probability of benefit to individuals in defined populations from a medical technology applied for a given medical problem under ideal conditions of use.

Effectiveness: Same as efficacy except that it refers to ". . . average conditions of use. "

This OTA definition of efficacy closely parallels BOB's definition of effectiveness shown in figure 6, and efficacy so defined is the term used in this chapter.



The 10 basic steps involved in BOB's vaccine product licensure and review process are shown in figure 7. Some of the procedures and processes that BOB uses to regulate the market introduction of vaccines resemble those that FDA's Bureau of Drugs (BOD) uses to regulate therapeutic prescription drugs. (See appendix 3.2.) Like BOD, BOB can require a manufacturer to submit for its approval an investigational new drug application (IND), which must be accepted before a U.S. manufacturer is permitted to test a new product in clinical trials. Also, like BOD, BOB can waive or modify the IND requirement if it believes that available foreign clinical trial data regarding a particular product are sufficient.

Unlike BOD, however, BOB does not use the new drug application (NDA) process to permit a manufacturer to market a product; instead, it issues establishment and product licenses. Before marketing a vaccine product, a manufacturer is required to obtain two types of licenses from BOB—a general manufacturing establishment license and a license for the particular product. Both types of licenses remain valid until suspended or revoked by FDA either for a particular cause or at the manufacturer's (voluntary) request.

For detailed discussion of each of the 10 steps shown in figure 7, including the sources of statutory and regulatory authority, see appendix 3.3. The types of safety and efficacy data and information on which BOB bases its evaluations of vaccines and other biological products are described in appendix 3.4.

BOB's use of premarketing data, criteria, standards, and methods to evaluate the clinical safety and efficacy of Merck's 14-valent pneumococcal capsular polysaccharide vaccine (PNEUMOVAX) prior to licensure is described below. Issues related to the heavy reliance on premarketing clinical testing and the comparatively small emphasis on structured, systematic, and comprehensive postmarketing evaluation are discussed further in chapter 6. Options for the Federal Government to strengthen postmarketing surveillance of licensed vaccines are described in chapter 7.

TYPES OF STUDIES USED TO EVALUATE THE SAFETY AND EFFICACY OF POLYVALENT PNEUMOCOCCAL VACCINE

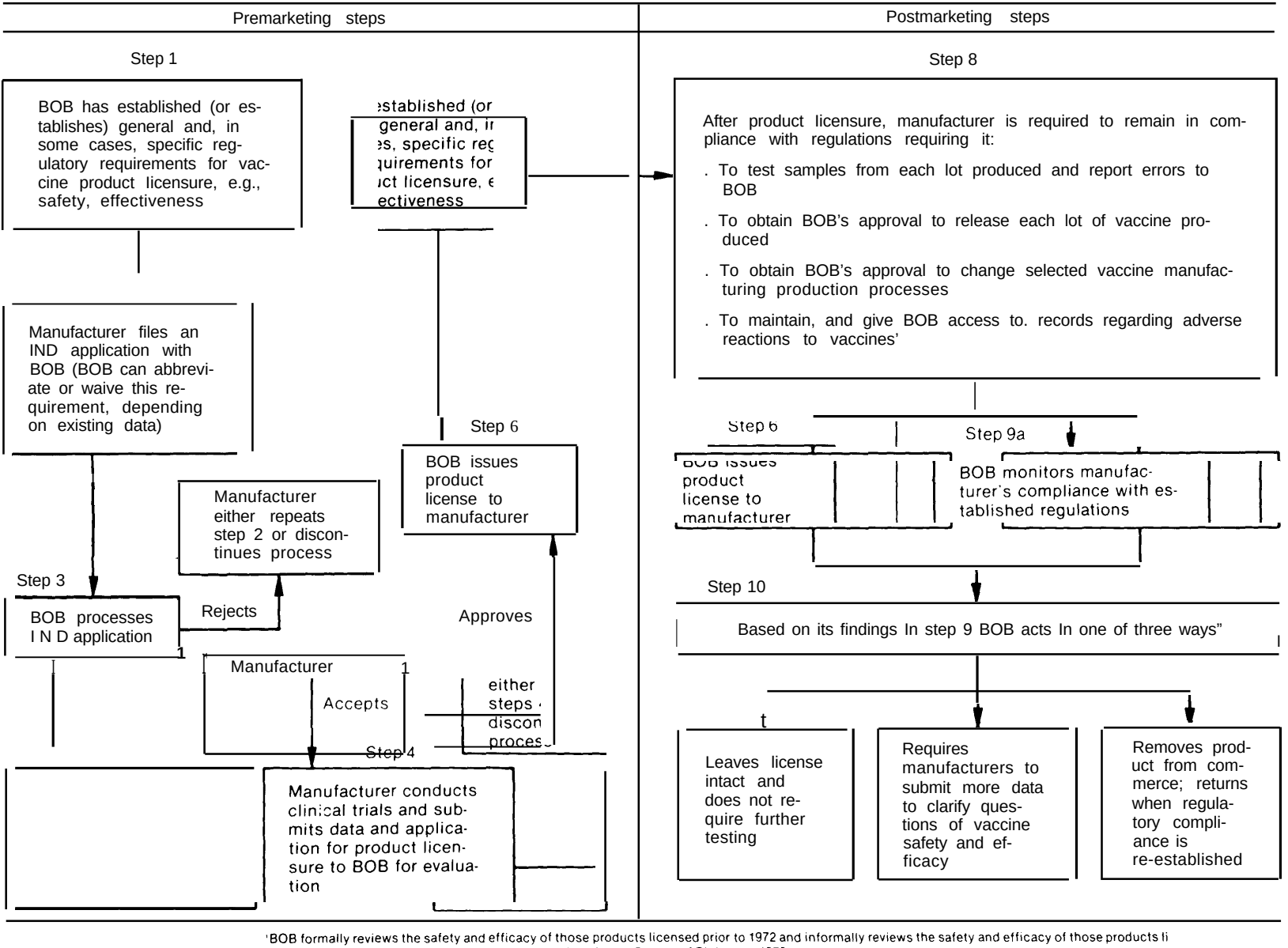
The safety and efficacy of 2-, 3-, 4-, and 6-valent pneumococcal capsular polysaccharide vaccines were demonstrated in three major clinical trials conducted independently by Lloyd Felton and G. M. Ekwurzel in the 1930's, Colin MacLeod in 1945, Paul Kaufman in 1947, and in the immunogenicity studies conducted by Michael Heidelberger in 1948. These investigations, discussed in appendix 1.1, were important benchmarks in the research and development of Merck Sharp and Dohme's (MSD) 14-valent vaccine. Because of differences in the chemical composition of the vaccines tested, however, most of these early trials did not generate data that BOB could use to evaluate the safety and efficacy of Merck's 14-valent vaccine.

To evaluate Merck's product, BOB required additional data, and for the most part, it relied on data from 26 studies conducted between 1967 and 1977. These 26 studies included three major types of investigations:

1. Epidemiologic studies to evaluate which types of pneumococci produce disease in the United States.

[1]The discussion in this chapter includes only those studies BOB used to evaluate polyvalent pneumococcal vaccine prior to licensure. Other studies of polyvalent pneumococcal vacines were conducted, but BOB did not rely on their data.

Figure 7.—BOB'S Vaccine Product Licensure Application and Review Process



'BOB formally reviews the safety and efficacy of those products licensed prior to 1972 and informally reviews the safety and efficacy of those products li
SOURCE: OTA's interpretation of information provided by the Bureau of Biologics. 1979.

2. **Immunogenicity studies** to determine pneumococcal vaccine's ability to stimulate the production of protective antibodies in humans.
3. Clinical trials to assess the level of the vaccine's clinical safety and efficacy in humans.

The three categories of studies used to evaluate the safety and efficacy of pneumococcal vaccine are described in appendix 3.5.

Altogether, the 26 studies on which BOB based its evaluation involved a total of approximately 60,000 subjects, about 23,000 (38 percent) of whom received some experimental pneumococcal vaccine. (See table 6.) Vaccines tested in these studies were 6-, 8-, 12-, 13-, or 14-valent pneumococcal polysaccharide vaccines produced in the United States by either EIi Lilly and Company or by Merck Sharp and Dohme (MSD).

Table 6.—Overview of the 26 Studies BOB Used To Evaluate Pneumococcal Vaccine

Sponsor/Study	Type of study[a]	Type of subjects	Number of subjects[b]	Year(s) of study
Industry[c]				
1. MSD (No. 315) (Smit)	Epidemiologic Efficacy Safety Immunogenicity	Foreign (South African)	983 vaccinees 2,036 controls	1973-75
2. MSD (No. 315A) (Smit)	Epidemiologic Efficacy Safety Immunogenicity	Foreign (South African)	718 vaccinees 1,493 controls	1974-76
3. MSD (No. 497)[d]. .	Immunogencity	Domestic	26 vaccinees	1977
4. MSD (No. 378)[e]. .	Immunogenicity in children	Foreign (Chilean)	4,000 vaccinees	1976
5. MSD(NO. 378D)[e]	Immunogenicity in children	Foreign (Chilean)	31 vaccinees	1976
6. MSD(NO. 337)[e]. .	Immunogenicity in children	Foreign (Chilean)	37 vaccinees	1976
7. MSD (No. 384)[f]. .	Immunogenicity Efficacy	Domestic	25 vaccinees	1976
8. MSD (No. 431)[f]. .	Immunogenicity Efficacy	Domestic	17 vacinees	1975
9. MSD (No. 482)[f]. .	Immunogenicity Efficacy	Domestic	13 vaccinees	1976
10. MSD (No. 454)[f]. .	Immunogenicity Efficacy	Domestic	23 vaccinees	1977
11. MSD9	Immunogenicity Safety	Domestic	20 vaccinees	1967
12. MSD/Papua[h] (Riley)	Epidemiologic Efficacy Safety Immunogenicity	Foreign (New Guinean)	5,946 vaccinees 6,012 controls	1973-76
13. Lederle (BB-IND 685) (Mufson).	Immunogenicity	Domestic	150 vaccinees 150 controls	1976
Subtotals . .	Epidemiologic (3 studies) Efficacy and Safety (8 studies) Immunogenicity (13 studies)	Foreign (6 studies) Domestic (7 studies)	11,989 vaccinees (foreign, 11, 715; domestic, 274) 9,691 controls (foreign, 9,541; domestic. 150)	1973-77

Footnotes appear at end of table

Table 6.—Overview of the 26 Studies **BOB Used To Evaluate Pneumococcal Vaccine—cont.**

Sponsor/Study	Type of studya	Type of subjects	Number of subjectsb	Year(s) of study
Government				
1. Austrian (Kaiser)	Efficacy Safety Immunogenicity	Domestic	6,850 vaccinees 6,750 controls	1972-76
2. Coulehan	Epidemiologic	Domestic	219 cases (no vaccinees)	1976
3. Austrian.	Immunogenicity	Domestic	21 vaccineesi	1976
4. Bentley.	Epidemiologic Immunogenicity	Domestic	110 vaccinees	1974
5. Ammann.	Efficacy Safety Immunogenicity	Domestic	178 vaccinees 106 controls	1977
Subtotals . .	Epidemiologic (2 studies) Efficacy and Safety (2 studies) Immunogenicity (4 studies)	Domestic (5 studies)	7,159 vaccinees 6,856 controls	1972-77
Academe				
1. Finland and Barnes	Epidemiologic	Domestic	12,049 cases (no vaccinees)	1935-74
2. Kaiser and Schaffner. . . .	Epidemiologic	Domestic	64 cases (no vaccinees)	*1968-72*
3. Shaperaand Matsen.	Epidemiologic	Domestic	62 cases (no vaccinees)	1961-70
4. Seeler.	Epidemiologic	Domestic	23 cases (no vaccinees)	1972
Subtotals. .	Epidemiologic (4 studies)	Domestic (4 studies)	12,198 cases (no vaccinees)	1935-77
Other				
1. Lund (Danish Government) .	Epidemiologic	Foreign	Unknown[k]	1955-70
2, Austrian (Chamber of Mines of South Africa. .	Epidemiologic (3 studies) Efficacy and Safety (3 studies) Immunogenicity (3 studies)	Foreign (South African) (3 studies)	4,000 vaccinees 8,000 controls	1972-76
Subtotals. .	Epidemiologic (4 studies) Efficacy and Safety (3 studies) Immunogenicity (3 studies)	Foreign (4 studies)	4,000 vaccinees 8,000 controls	1955-76

Footnotes appear at end of table

Table 6.—Overview of the 26 Studies BOB Used To Evaluate Pneumococcal Vaccine—cont.

Sponsor/Study	Type of study[a]	Type of subjects	Number of subjects[b]	Year(s) of study
SUBTOTALS	Epidemiologic (13 studies) Efficacy and Safety (8 studies) Immunogenicity (20 studies)	Foreign (10 studies) Domestic (16 studies)	23,148 vaccinees (foreign, 15,715; domestic, 7,433) 24,547 controls (foreign, 1 7,541; domestic, 7,006) 12,417 cases	1935-77
TOTALS	Epidemiologic, Efficacy and Safety, Immunogenicity (26 studies)[j]	Foreign and Domestic (26 studies)[j]	60,112 subjects	1935-77

[a] In "Efficacy" studies cited, investigators measured the reduction in the incidence of pneumococcal disease among vaccinees in controlled clinical trials
[b] Some epidemiologic studies listed report only cases of pneumococcal pneumonia. In these studies, there were no vaccinated or control subjects
[c] Except for the study by Lederle, all these studies were funded entirely or partially by Merck Sharp and Dohme (MSD).
[d] The results of Merck's immunogenicity study No. 497 were not published.
[e] The results of these Merck immunogenicity studies were reported by Borgon
[f] The results of these Merck immunogenicity studies were reported by Weibel
[g] The results of this Merck study were not published.
[h] This study was cosponsored by Merck Sharp and Dohme and the Department of Public Health, Papua, New Guinea.
[i] All these U.S studies were funded or assisted in some way by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
[j] Austrian conducted vaccine immunogenicity studies involving over 1,000 vaccinees under contract with NIAID. The extent to which data from these investigations were used by BOB was not ascertained for this report.
[k] The total number of cases reported in Dr. Lund's investigation were not calculated for this report.
[l] This number refers to major studies In some studies, two or three types of investigations, (e.g., epidemiologic, efficacy and safety, and immunogenicity) were conducted.

SOURCE OTA's interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal investigators of included studies, 1979.

Ten of the 26 studies were conducted in foreign countries: five in South Africa, three in Chile, one in New Guinea, and one in Denmark. Foreign studies involved about 33,000 subjects (55 percent of the total study population), including some 16,000 vaccinees (70 percent of the total vaccinated).

Primary sponsors were Merck Sharp and Dohme (the first vaccine manufacturer licensed to produce pneumococcal vaccine in the United States), the National Institute of Allergy and Infectious Diseases (NIAID), and the Chamber of Mines of South Africa. Other sponsors included academic institutions in the United States, the Danish Government, and the Department of Public Health, Papua, New Guinea.

RESULTS OF PREMARKETING CLINICAL TRIALS OF PNEUMOCOCCAL VACCINE[2]

Clinical Safety

The types of adverse reactions produced by vaccines can be categorized as follows:

Local reactions: These reactions include pain, redness, and swelling at the vaccine injection site. Such reactions do not involve other areas of the body and are usually minor.

[2] Data from the 13 epidemiologic studies of Pneumococcal pneumonia and the 20 studies BOB used to assess the immunogenicity of experimental polysaccharide polyvalnt pneumococcal vaccines are not summarized in this report. For these data, consult the references cited for each study in table **6.**

Systemic reactions: These reactions include perturbations in one or more organ systems and can affect one or more areas of the body. Such reactions range from fevers to allergic reactions; their severity can be mild and short-lived, severe and long-lasting, or sometimes even fatal.

Fatal reactions from the use of pneumococcal vaccine have not been reported.

The results of the eight clinical trials and one other report (Weibel, 1977) that BOB used to assess the level of safety of experimental polyvalent pneumococcal polysaccharide vaccines are presented in table 7. As shown in this table, in the five clinical trials conducted in South Africa (two by Merck, three by Robert Austrian), investigators reported quite low rates of adverse reactions. The incidence of local reactions reported in these studies was around 1 to 2 percent; fevers were not commonly reported; and no severe or fatal reaction was reported (Austrian, et al., 1976; Smit, 1977). In his investigation in New Guinea, I. D. Riley studied adverse reactions in a subpopulation of 133 vaccinees (comprising 2 percent of his total study population), and reported a 27 percent incidence of local reactions and a 7 percent incidence of mild fevers (Riley, 1977). Riley further reported that 75 percent of these 133 vaccinees experienced no adverse reactions.

In an NIAID-sponsored study among 180 vaccinees in the United States, Arthur Ammann reported only one case of mild fever (Ammann, 1977). Austrian, in another NIAID-sponsored U.S. study of 6,850 vaccinees, reported a 40 percent incidence rate of

Table 7.— Results of Premarketing Safety Studies of Pneumococcal Vaccine

	Number of vaccinees[a]		Rate of reported reactions[b]			
Sponsor	Foreign	Domestic	Local[c]	Fever	No reactions	Severe systemic
Industry[d]						
1. MSD (No. 315) (South Africa)	983		1-2 percent	Low frequency	High frequency	None
2. MSD (No. 315A) (South Africa)	718		1 percent	Low frequency	High frequency	None
3. Riley[e] (New Guinea)	5,946 (133)[a]		27 percent	7 percent (mild)	75 percent	None
4. Weibel (No. 384, 431, 454, 482) (USA)		92	86-98 percent (1 case-severe)	14-40 percent (1 case-high)	14 percent	None
Government[f]						
1. Austrian (Kaiser-USA)		6,850	40 percent	3.4 percent (mild)	60 percent	None
2. Ammann (USA)		178	Unknown	1 case (mild)	Unknown	None
Other[g]						
1, Austrian (South Africa) (3 trials)	4,000		1 percent	1 percent	99 percent	None
Subtotals	17,647	7,120				
Total	18,767					

[a]The exact number of vaccinees observed for adverse reactions in most of these studies is unknown. Numbers refer to the total number of vaccinees in each study, but in some of the studies, only some of the vaccinees may have been observed for adverse reactions. In Riley's New Guinea study, for example, only 133 of 5,946 vaccinees were observed for adverse reactions.
[b]The inconsistent manner in which data for different studies are displayed in this table reflects the manner in which clinical investigators reported these data.
[c]Local reactions include pain, redness, and swelling at the vaccine injection site.
[d]These studies were sponsored by Merck Sharp and Dohme (MSD).
[e]This study was cosponsored by Merck Sharp and Dohme and the Department of Public Health, Papua, New Guinea.
[f]These studies were sponsored at least in part by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes Of Health (NIH)
[g]These studies were sponsored by the Chamber of Mines of South Africa.

SOURCE: OTA's Interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal investigators of included studies

local reactions and a 3 percent rate of mild fevers; 60 percent of the vaccinees in the Austrian study experienced no adverse reactions (Austrian, et al., 1976).

In a group of small Merck Sharp and Dohme studies (not clinical trials) also conducted in the United States, Robert Weibel reported much higher incidence rates of adverse reactions (Weibel, 1977). For example, among 92 vaccinees in four studies, 86 to 98 percent reported experiencing local reactions (one case was severe), and 14 to 40 percent reported fever (one case was severe).

In the eight clinical trials that generated data which BOB used to evaluate the safety and efficacy of the currently licensed pneumococcal vaccine, a total of six different vaccine products were used. These products were a 6-valent, a 12-valent, and a 14-valent pneumococcal vaccine produced by Merck Sharp and Dohme, and a 6-valent, an 8-valent, and a 13-valent vaccine produced by Eli Lilly.

Clinical Efficacy

The primary criterion investigators in the eight clinical trials used to evaluate pneumococcal vaccine's clinical efficacy was the incidence of pneumococcal pneumonia (or in some cases, bacteremia) caused by the types of pneumococci represented in the vaccine. The incidence of either pneumococcal pneumonia or bacteremia among vaccinees was compared to the incidence of such disease among control subjects. The results of these eight trials are presented in table 8.

Table 8.—Results of Premarketing Efficacy Trials of Pneumococcal Vaccine

Sponsor	Type of vaccine	Number of subjects	Reduction in the incidence of diseasea among vaccine recipients: Pneumococcal pneumonia	Pneumococcal bacteremia
Industry[b]				
1. MSD (No. 315) (South Africa)	6-valent (MSD)	983 vaccinees 2,036 controls	76 percent	Unknown
2. MSD (No. 315A) (South Africa)	12-valent (MSD)	718 vaccinees 1,493 controls	92 percent	Unknown
3. RileyC (New Guinea)	14-valent (MSD)	5,946 vaccinees 6,012 controls	Unknown[d]	Unknown
Government				
1. Austrian (Kaiser-USA)	13-valent (Lilly)	6,850 vaccinees 6,750 controls	Unknown	100 percent[f]
2. Ammann (USA)	8-valent (Lilly)	77 vaccinees 106 controls	100 percent[g]	
Other[h]				
1. Austrian (South Africa) (3 trials)	6-valent, 13-valent (Lilly)	4,000 vaccinees 8,000 controls	78.5 percent[i]	82.3 percent
Total		18,574 vaccinees 24.397 controls		

[a]Disease means either pneumococcal pneumonia or bacteremia caused by one of the types of pneumococci represented in the experimental vaccine
[b]These studies were sponsored by Merck Sharp and Dohme
[c]This study was cosponsored by Merck Sharp and Dohme and the Department of Public Health, Papua, New Guinea
[d]In this study, an 18 percent reduction in incidence of lower respiratory tract infection (LRTI) and a 22 percent reduction in overall death rate were reported
[e]These studies were sponsored at least part by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
[f]Four cases occurred among controls, none among vaccinees.
[g]Eight cases occurred among controls, none among vaccinees
[h]These studies were sponsored by the Chamber of Mines of South Africa
[i]This reduction was reported in only one trial involving 1,493 pneumococcal vaccinees and 3.007 control subjects

SOURCE OTA'S Interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal Investigators of included studies, 1979

In Merck study No. 315, a 6-valent vaccine was tested in South Africa. The type-specific (i.e, caused by one of the six types of pneumococci represented in the vaccine) pneumococcal pneumonia incidence rate among nearly 1,000 vaccinees in this study was 76 percent lower than the rate among 2,000 control subjects (Smit, 1977). When a 12-valent vaccine was tested in a similar clinical trial in South Africa, MSD No. 315A, a 92 percent reduction in the incidence rate of type-specific pneumococcal pneumonia was reported (Smit, 1977).[3]

In three South African clinical trials sponsored by the Chamber of Mines of South Africa and conducted by Austrian, a total of 4,000 test subjects were vaccinated with polyvalent pneumococcal vaccines made by Eli Lilly, and 8,000 subjects were used as controls (Austrian, et al., 1976). BOB used two findings from these trials to evaluate the clinical efficacy of the vaccine. First was the finding in one trial involving a 13-valent vaccine that the incidence rate for type-specific putative pneumococcal pneumonia was 78.5 percent lower among 1,493 vaccinees than the rate among 3,007 controls. Second was the finding that, when data were combined from all three trials, the incidence rate of type-specific pneumococcal bacteremia among the 4,000 vaccinees was 82.3 percent lower than the rate among the 8,000 controls; 10 cases of type-specific bacteremia occurred in pneumococcal vaccinees, while 113 cases occurred among control subjects.

In Riley's New Guinea study, cosponsored by Merck and the Papua Department of Public Health, about 6,000 persons received an experimental 14-valent pneumococcal vaccine, and another 6,000 persons received a placebo (Riley, 1977). Investigators in this clinical trial did not measure the difference between vaccinees and controls in the incidence of type-specific pneumococcal pneumonia or bacteremia. Instead, they measured the difference in the incidence of lower respiratory tract infection (LRTI). The incidence of LRTI among pneumococcal vaccinees was only 18 percent lower than the incidence among control subjects.

In the NIAID-sponsored clinical trial conducted by Austrian at the San Francisco Kaiser Permanence Medical Center, 6,850 test subjects received experimental 13-valent pneumococcal polysaccharide vaccine, and 6,750 control subjects received a placebo vaccine (Austrian, May 28, 1976). The attack rate of respiratory disease caused by the types of pneumococci represented in the vaccine was too low in the experimental and control groups to yield statistically significant data regarding the clinical efficacy of the vaccine in preventing pneumococcal pneumonia. BOB, however, did use incidence data for pneumococcal bacteremia to help assess the efficacy of the vaccine. Four cases of bacteremia occurred in the control population, and no cases occurred in the test population.

In another NIAID-sponsored trial, also conducted in San Francisco, Ammann administered an 8-valent pneumococcal polysaccharide vaccine made by Eli Lilly to 77 children with sickle-cell disease. He then compared the incidence of pneumococcal infections among these children to that among 106 unvaccinated children with sickle-cell disease (Ammann, 1977). During a 2-year followup period, Ammann found eight cases of pneumococcal disease among the unvaccinated controls and no cases among vaccinees.

The studies BOB used to evaluate the clinical safety and efficacy of pneumococcal vaccine prior to licensure are described in detail in appendix 3.6.

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[3]The diagnosis of pneumococcal pneumonia initially was made on the basis of clinical criteria (e.g., cough, fever, purulent, rusty, or bloody sputum, rales, bronchial breathing, and localized chest pain on percussion). In any test subject having three or more of these symptoms or signs, investigators conducted a chest X-ray and collected samples for further laboratory diagnostic study. Typing of pneumococci was performed using the Quellung reaction. Sera were tested for antibodies by a standard radioimmunoassay.

BOB'S PRELICENSING EVALUATION OF PNEUMOCOCCAL VACCINE

Based on its analysis of data from the studies discussed above, BOB issued the statements below regarding the public need for, as well as the safety and efficacy of, Merck's 14-valent pneumococcal capsular polysaccharide vaccine (PNEUMOVAX). These statements were contained in BOB's summary of its basis for approving licensure of this product (U.S. Ex. Br., BOB, 1977):

Public Need

Pneumococci cause serious disease in individuals of all ages. As individuals mature over *50* years, the attack rate of pneumococcal disease increases. Individuals who have had their spleens removed or have malfunctioning spleens, 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 other acquired resistance to many other antibiotics. *Thus, prevention of* ***this disease seems worthwhile.***

Environmental Impact Analysis Report

The cost of producing the vaccine, the waste products from the vaccine, and the cost of the vaccine are not considered to have a deleterious environmental impact. It is anticipated that a favorable environmental impact upon the Nation's health will be induced by the vaccine.

Safety

Adverse reactions such as local swelling, pain or erythema, occur in approximately *5-15%* of vaccine recipients. These reactions are considered minor and do not interfere with the benefit/risk provided by this vaccine for the patient.

In clinical trials of this product, as well as comparable products made by Eli Lilly and Company under contract for the National Institute of Allergy and Infectious Diseases, and capsular polysaccharides made by E. R. Squibb & Sons, Inc., and individual investigators in the 1930's and 1940's, approximately 20,000-30,000 individuals have been vaccinated. There have been no reports of immediate or long range toxic effects.

There are no deleterious effects of this capsular polysaccharide vaccine when injected in appropriate doses in laboratory animals. At very high doses (at least logarithms in excess of the human dose) or extraordinarily low doses (two logarithms less than the human dose), a suppressive effect upon the specific immune response to the polysaccharide may be induced. This phenomenon has not been observed with pneumococcal capsular polysaccharides in humans or following disease with the individual types of organisms.

Efficacy

Indications for use: For the prevention of pneumococcal pneumonia and/or bacteremia in individuals older than 2 years of age.

The mechanism by which the vaccine exerts its protective effect is the induction of serum antibodies. . . . individuals less than 2 years of age, pregnant women, or individuals with primary or treatment-induced immunodeficiency states may not respond with sufficient amount of antibody to have the protective immunity . . .

> . . . antibody response to each type is not inhibited by their polyvalent formulation. The antibody response has been shown to be the protective moiety and can be induced with regularity in at least 80-100% of all vaccine recipients over the age of 2 years. A similar response occurs in those well into the 70's and 80's as well as healthy individuals who do not have spleens or have malfunctioning spleens, such as seen in excessive hemolytic states as sickle-cell anemia and in individuals who have chronic alcoholism as a disability.

The Code of *Federal Regulations* contains the following mandate (21 CFR 601 .25):

> The benefit-to-risk ratio of biological product shall be considered in determining safety and efficacy.

After BOB separately analyzed data regarding the safety and efficacy of pneumococcal vaccine, it considered these data together to determine the relative benefits and risks of the vaccine under anticipated conditions of use. The potential benefits of pneumococcal vaccine, BOB apparently believed, outweighed its risks.

On the basis of BOB's evaluation, on November 21, 1977, FDA issued Merck Sharp and Dohme a license to market its 14-valent pneumococcal capsular polysaccharide vaccine (PNEUMOVAX). FDA-approved statements for the package insert of Merck's product are shown in figures 8 (Public Need), 9 (Safety), and 10 (Efficacy). Presumably, the same statements will appear on the package insert for Lederle's new polysaccharide pneumococcal vaccine (PNU-IMUNE), which FDA licensed on August 15, 1979.

POSTMARKETING DATA REGARDING THE SAFETY AND EFFICACY OF PNEUMOCOCCAL VACCINE

Merck's 14-valent pneumococcal vaccine (PNEUMOVAX) appeared on the U.S. market in February of 1978. The company reported that between February and September of 1978, roughly 1.6 million doses of this vaccine were distributed in the United

Figure 8.—FDA-Approved Statements Regarding the Public Need for Pneumococcal Vaccine (PNEUMOVAX)

Pneumococcal infection is a leading cause of death throughout the world and a major cause of pneumonia, meningitis, and otitis media. The exact incidence of pneumococcal infection is not known. On the basis of the limited epidemiological data obtained from studies in municipal hospitals where the incidence might be higher than that found in the average population, it is estimated that there are annually 200,000 to 1,000,000 cases of pneumococcal pneumonia in the United States, and between 13,200 and 66,000 deaths resulting therefrom. Thus, the attack rate for pneumococcal pneumonia is estimated to be between 1 and 5 cases per 1,000 persons per year, and death is *estimated* to occur in about 1 of 15 cases. Based on these same data, about 25 percent of all persons with pneumococcal pneumonia develop bacteremia. Death occurs in about 28 percent of these bacteremic patients more than 50 years of age.

In the United States, pneumococcal meningitis occurs principally in young children with annual rates of about 3 to 11 per 100,000 children less than 5 years old. Within the first 2 years of life, about 15 to 20 percent of all children develop otitis media caused by pneumococci, and 50 percent of all children develop such illness within the first 10 years of life (see under INDICATIONS).

Invasive pneumococcal disease causes high morbidity and mortality in spite of effective antimicrobial control by antibiotics. These effects of pneumococcal disease appear due to irreversible physiologic damage caused by the bacteria during the first 5 days following onset of illness, and irrespective of antimicrobial therapy. Older persons, individuals with chronic debilitating diseases, and persons with absent or impaired splenic function, including those with homozygous sickle-cell anemia and sickle thalassemia, are especially susceptible to severe pneumococcal disease.

SOURCE: Package Insert, PNEUMOVAX, Merck Sharp and Dohme, 1979.

Figure 9.—FDA-Approved Statements Regarding the Safety of Pneumococcal Vaccine (PNEUMOVAX)

PRECAUTIONS

Any febrile respiratory illness or other active infection is reason for delaying use of PNEUMOVAX, except when, in the opinion of the physician, withholding the agent entails even greater risk.

Caution and appropriate care should be exercised in administering PNEUMOVAX to individuals with severely compromised cardiac and/or pulmonary function in whom a systemic reaction would pose a significant risk.

Patients who have had episodes of pneumococcal pneumonia or other pneumococcal infection in the preceding 3 years may have high levels of pre-existing pneumococcal antibodies which may result in increased reactions to PNEUMOVAX, mostly local but occasionally systemic. Caution should be exercised if such patients are considered for vaccination with PNEUMOVAX.

Available data suggest that revaccination before 3 years may result in more frequent and severe local reactions at the site of injection, especially in persons who have retained high antibody levels (see DOSAGE AND ADMINISTRATION).

Children under 2 years of age may not obtain a satisfactory antibody response to some pneumococcal capsular types. Therefore, the vaccine should not be used in this age group.

ADVERSE REACTIONS

Local erythema and soreness at the injection site, usually of less than 48 hours duration, occurs commonly; local induration occurs less commonly. In a study of PNEUMOVAX (containing 14 capsular types) in 26 adults, 24 (92 percent) showed local reaction characterized principally by local soreness and/or induration at the injection site within 2 days after vaccination.

Low grade fever (less than 100.9° F) occurs occasionally and is usually confined to the 24-hour period following vaccination. Although rare, fever over 102° F has been reported.

Reactions of greater severity, duration, or extent are unusual. Rarely, anaphylactoid reactions have been reported . . .

WARNINGS

Intradermal administration may cause severe local reactions.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine. Epinephrine injection (1:1000) must be immediately available should an acute anaphylactoid reaction occur due to any component of the vaccine.

Do not give PNEUMOVAX to pregnant females. The possible effects of the vaccine on fetal development are unknown.

SOURCE: Package Insert, PNEUMOVAX, Merck Sharp and Dohme, 1979

States for general use. Approximately 1.0 million doses probably were administered (Kasdin, 1979).

Neither the Federal Government nor the pharmaceutical industry systematically surveys vaccinees to determine the incidence of adverse reactions to licensed vaccines. Since Merck's pneumococcal vaccine has been in general use, however, a few reports of serious adverse reactions have voluntarily been made publicly available. Sporadic reporting in clinical literature, for example, has revealed at least three cases of severe fever associated with the use of this product (Uhl, 1978; Semel, 1979). In addition, reports vol - untarily submitted to the Center for Disease Control (CDC) by Merck Sharp and Dohme and by physicians administering the vaccine, as of September 1978, included six cases of possible anaphylaxis (severe allergic reaction), four cases of fever (1000 F), and nine cases of severe local reactions (Broome, 1978). Additional cases of adverse reactions to pneumococcal vaccine may have been reported through CDC's passive and voluntary vaccine adverse reaction monitoring system. (See appendix 3.7.)

Figure 10.—FDA-Approved Statements Regarding the Efficacy of Pneumococcal Vaccine (PNEUMOVAX)

INDICATIONS

PNEUMOVAX is indicated for immunization against pneumonia and bacteremia, caused by those types of pneumococci included in the vaccine, in all persons 2 years of age or older in whom there is an increased risk of morbidity and mortality from pneumococcal pneumonia. These include: 1) persons having chronic physical conditions such as chronic heart disease of any etiology, chronic bronchopulmonary diseases, chronic renal failure, and diabetes mellitus or other chronic metabolic disorders; 2) persons in chronic care facilities; 3) persons convalescing from severe disease; 4) persons 50 years of age or older.

Preliminary data suggest the vaccine is efficacious for preventing severe pneumonic disease and bacteremia in persons over 2 years of age with sickle-cell anemia and in individuals who have had a splenectomy or who have impaired splenic function, and in pediatric patients over 2 years of age with nephrotic syndrome. It is expected also that the vaccine will be found effective in preventing pneumococcal meningitis of bacteremic origin. However, PNEUMOVAX may not be effective in preventing infection resulting from basilar skull fracture or from external communication with cerebrospinal fluid. Studies are underway to determine the effectiveness of the vaccine for preventing pneumococcal otitis media in infants.

Presently, there are 83 known pneumococcal capsular types. However, the preponderance of pneumococcal diseases is caused by only some capsular types. For example, a 10-year (1952-1962) surveillance at a New York medical center showed that 56 percent of all deaths due to pneumococcal pneumonia were caused by 6 capsular types and that approximately 78 percent of all pneumococcal pneumonias were caused by 12 capsular types. Such unequal distribution of pneumococcal capsular types causing disease has been shown throughout the world. It is on the basis of this information that the pneumococcal vaccine is composed of 14 capsular types.

It has been established that the purified pneumococcal capsular polysaccharides induce antibody production and that such antibody is effective in preventing pneumococcal disease. PNEUMOVAX consists of 14 different capsular polysaccharides which represent at least 80 percent of pneumococcal disease isolates in the United States and Europe. Studies in humans have demonstrated the immunogenicity (antibody-stimulating capability) of each of the 14 capsular types when tested in polyvalent vaccines. Adults of all ages and children of 2 years of age or older responded immunologically to the vaccines. In a recent study of PNEUMOVAX, at least 90 percent of all adults showed a fourfold or greater increase in type-specific antibody for each vaccine capsular type . . .

The duration of protective effect of PNEUMOVAX is presently unknown, but it has been shown in previous studies with other pneumococcal vaccines that antibody induced by the vaccine may persist for as long as 5 years. Type-specific antibody levels induced by PNEUMOVAX have been observed to decline over a 20-month period of observation, but remain significantly above prevaccination levels in almost all recipients who manifest an initial response.

Because of the decline in antibody levels, revaccination may be considered. Available data suggest that revaccination should not be carried out at less than 3-year intervals so as to minimize the frequency and severity of local reactions, especially in persons who have retained high antibody levels. Long-term surveillance of antibody levels in immunized individuals is continuing . . .

WARNINGS

PNEUMOVAX will not immunize against capsular types of pneumococcus other than those contained in the vaccine (see above).

If the vaccine is used in persons receiving immunosuppressive therapy, the expected serum antibody response may not be obtained.

Children less than 2 years of age do not respond satisfactorily to the capsular types of PNEUMOVAX that are most often the cause of pneumococcal disease in this age group. Accordingly, PNEUMOVAX is not recommended in this age group.

Patients with Hodgkin's disease who have received extensive chemotherapy and/or nodal irradiation have been shown to have an impaired antibody response to a 12-valent pneumococcal vaccine. Because, in some intensively treated patients, administration of that vaccine depressed pre-existing levels of antibody to some pneumococcal types, PNEUMOVAX is not recommended at this time for patients who have received these forms of therapy for Hodgkin's disease.

SOURCE: Package Insert, PNEUMOVAX, Merck Sharp and Dohme, 1979.

In 1978, Nicholas Fiumara and George Waterman conducted a field study of the licensed 14-valent pneumococcal vaccine among 13,336 senior citizens and patients rehabilitating in various health care centers in Massachusetts (Fiumara, 1979). According to the investigators, vaccinees were monitored for adverse reactions for 48 hours subsequent to vaccination. During this observation period, nursing staffs in health care facilities reportedly recorded complaints that vaccinees volunteered about local reactions (at the site of injection) and took each vaccinee's body temperature twice daily. Reactions were reported in about 6 percent of 12,529 vaccinees: About 5.3 percent (715) experienced local reactions (soreness), and about 0.7 percent (92) had fevers, most of which *were* quite mild (100 ^{0} to **100.90** F). It is difficult to determine from the literature report of this study the extent to which vaccinees were monitored for severe systemic reactions to the vaccine, but no such reactions were reported.

Since pneumococcal vaccine has been marketed, at least five reports of vaccine failure have appeared in the medical literature (Overturf, 1979; Minor, 1979; Giebink, 1979; Preheim, 1978; Ahonkhai, 1979). In each of these reports, a person vaccinated with the licensed 14-valent product developed a pneumococcal infection caused by one of the types of pneumococci represented in the vaccine. Some of these vaccinees were healthy, although at least three had sickle-cell disease, one had Hodgkin's disease, and one had no spleen.

By themselves, these cases do not provide a sufficient data base for a comprehensive postmarketing evaluation of the vaccine's efficacy. In premarketing clinical trials, pneumococcal vaccine was shown to be about 80 percent effective. These newly reported cases may merely represent the 20 percent of vaccinees that would not be expected to be effectively protected by the vaccine. These cases may, however, represent vaccine failures that were not expected and may indicate that the vaccine is less efficacious, at least in high risk populations, than the 80 percent level projected on the basis of efficacy data from premarketing clinical trials. Further postmarketing clinical research is needed to more fully assess the efficacy of this vaccine in general use among healthy, as well as high risk, vaccinees.

One postmarketing literature report regarding the efficacy of Merck's new vaccine resulted in a change in the wording of the FDA-approved package insert. In August 1978, George Siber and associates reported a demonstrated impaired antibody response to pneumococcal vaccine in 53 patients previously treated for Hodgkin's disease (a form of cancer in the lymph glands) (Siber, 1978). As a result of this finding, BOB and Merck Sharp and Dohme agreed that the following language should be added to the vaccine's package insert:

> Patients with Hodgkin's disease who have received extensive chemotherapy and/or nodal irradiation have been shown to have an impaired antibody response to a 12-valent pneumococcal vaccine. Because, in some intensively treated patients, administration of that vaccine depressed pre-existing levels of antibody to some pneumococcal types, PNEUMOVAX is not recommended at this time for patients who have received these forms of therapy for Hodgkin's disease.

As mentioned in chapter 2, the National Institute of Allergy and Infectious Diseases (NIAID) is currently facilitating approximately 35 studies of the safety, Clinical efficacy, and immunogenicity of pneumococcal polysaccharide vaccines in specialized populations. NIAID is not funding these studies directly; instead, it is providing the assistance of its professional staff to researchers (mostly in academe) who wish to test some aspect of the vaccine. This Institute also finances antibody assays for these studies through a contract with a laboratory at the State University of New York (SUNY), Downstate Med-

ical Center, Brooklyn. It also is coordinating the dispersement to clinical investigators of pneumococcal vaccines, often donated, from the manufacturer.

Since licensure of the new 14-valent pneumococcal vaccine, NIAID has facilitated about 25 investigations of the vaccine's use among high risk populations: 8 involve splenectomized persons, 9 involve children with sickle-cell disease, 9 involve patients with various forms of cancer, and 13 involve patients with other types of medical problems.[4] These studies combined involve a total of about 2,800 subjects. Results from these studies will be made public, and some data will be available in the fall of 1979.

The Bureau of Biologics (BOB) since licensure has continued to seek and coordinate information regarding pneumococcal vaccine's safety and efficacy (Robbins, 1979). For example, BOB has sponsored three workshops at which new scientific data relating to the vaccine's safety, immunogenicity, and clinical efficacy were presented and discussed by prominent researchers. Further, BOB has incorporated selected new scientific and clinical findings into its evaluation and labeling requirement of the licensed product (e.g., regarding vaccination of patients with Hodgkin's disease). To coordinate information received from practitioners regarding adverse reactions to the vaccine, BOB participates in a voluntary arrangement with CDC, Merck Sharp and Dohme, and NIAID. Many, if not most, of BOB's postmarketing product evaluation activities result from the professional concerns and incentives of BOB's scientific personnel, rather than from statutory or regulatory authority or responsibility.

In Johannesburg, South Africa, Michael Jacobs and associates studied the emergence of new strains of pneumococci that are resistant to certain antibiotics (Jacobs, 1978). In particular, these investigators reported resistance to some antibiotics among Types 6A and 19A pneumococcal isolates. Antibiotic-resistant Type 6B pneumococci also have been reported (U.S. Ex. Br., CDC, 1979). Increasing numbers and growing patterns of types of pneumococci that are resistant to antibiotics enhance the usefulness of the new vaccine. Type 6A is represented in the vaccine, but Types 6B and 19A are not. Vaccine Type 19F, however, probably would confer protection against most infections caused by Type 19A. Type 6A would likely protect against Type 6B infections. Jacobs has suggested that extensive antibiotic resistance among types of pneumococci not currently in the licensed vaccine could serve as a criterion for altering the vaccine's composition.

LIMITATIONS OF PREMARKETING EVALUATIONS OF THE SAFETY AND EFFICACY OF PNEUMOCOCCAL VACCINE

Inherent Limitations of Premarketing Clinical Studies

In theory, every clinical trial is designed to assess both safety and efficacy. In fact, the degree of assessment of these two characteristics largely depends on the extent to which investigators in a particular trial focus on one characteristic or the other. Thus, reports regarding the number and types of adverse reactions to vaccines often reflect the intensity of researchers' efforts to evaluate vaccine safety.

Even when investigators design their clinical trials to emphasize the detection of adverse reactions, however, their ability to detect certain types of adverse reactions may be limited. Differences in local and systemic reaction rates reported in various studies may be influenced by a number of factors (Parkman, 1979):

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[4]Some; these studies involve two or more of these high risk populations. The total of the numbers cited for each high risk population, therefore, exceeds 25.

> Differences in local and systemic reaction rates in various studies are not unexpected; assessment of objective reactions depends, among other factors, on the timing and frequency of observation, and on subjective reactions or the judgment of the investigators.

A greater problem with evaluating the safety of vaccines in premarketing clinical trials, however, stems from the fact that most of these trials are conducted over 1- to 3-year periods (sometimes less) and usually do not involve large sample populations. As a result, reported adverse reactions to vaccines tested in premarketing clinical trials tend to be limited to acute and commonly occurring reactions. Two types of adverse reactions, in particular, frequently escape detection in premarketing clinical tests:

1. Adverse reactions that rarely occur, and
2. Adverse reactions that occur with delayed onset.

These limitations of premarketing clinical trials are illustrated in the case of pneumococcal vaccine. At least six investigations to evaluate the safety and efficacy of pneumococcal vaccines were conducted in this country. U.S. investigations included two clinical trials, Austrian's NIAID-sponsored study at the San Francisco Kaiser Permanence Medical Center (Austrian, et al., 1976), and Ammann's study in sickle-cell children (Ammann, 1977). The other four investigations, not clinical trials, were Merck studies No. 384, 431, 454, and 482 (Weibel, 1977). Differences in findings concerning adverse reactions to pneumococcal vaccine were substantial. Austrian reported that about 40 percent of his 6,850 vaccinated subjects experienced local reactions and another 3.4 percent developed a mild fever. In Merck studies No. 384, 431, 454 and 482, involving a total of 92 subjects, Weibel reported incidence rates for local reactions of 86 to 92 percent and incidence rates for fever of 14 to 40 percent. Ammann reported only one case of mild fever among the 180 vaccinees in his study. Austrian and Ammann each used different vaccines produced by Eli Lilly, and Weibel used vaccines manufactured by Merck Sharp and Dohme.

The total number of vaccinees involved in premarketing clinical trials of pneumococcal vaccine, including 15,715 foreign subjects and 7,433 domestic subjects, was about 23,000. (See table 6.) Vaccine safety was evaluated in about 18,800 vaccinees. (See table 9.) Relative to the size of sample populations used to evaluate other vaccines prior to marketing, the population of 23,000 vaccinees who received pneumococcal vaccine in premarketing testing is large. Yet as one BOB official commented (Parkman, 1979):

> Clearly, one cannot reliably predict six possible cases of anaphylaxis in about one million vaccinees on the basis of an experience with **23,000.**

Data from studies involving 23,000 vaccinees cannot be used alone as the basis for predictions of the incidence of rare adverse reactions that might result if pneumococcal vaccine were to be used, for example, in a large public immunization program.

Vaccine Testing Among Foreign Populations

In accordance with the law and FDA regulations, a vaccine manufacturer must demonstrate the efficacy of a new vaccine product in clinical trials before FDA will license the product. To demonstrate **a** new vaccine's clinical efficacy, investigators must test the product in a defined population in which the incidence or prevalence of the target disease can be measured.

Because of the relatively low reported incidence of pneumococcal pneumonia in the United States (1 to 5 cases per 1,000 persons per annum), assessment of pneumococcal vaccine's clinical efficacy in this country would have been very time-consuming and ex-

Table 9.-Number of Subjects Involved in Premarketing Safety Studies of Pneumococcal Vaccine

Sponsor	Vaccinees		Controls	
	Foreign	Domestic	Foreign	Domestic
Industry[a]				
1. MSD (No. 315) (South Africa)	983	—	2,036	—
2. MSD (No. 315A) (South Africa)	718	—	1,493	—
3. Riley[b] (New Guinea)	5,946	—	6,012	—
4. Weibel (No. 384,431,454, 482) (USA)	–	92	—	
Subtotal	7,647	92	9,541	—
Government				
1. Austrian (Kaiser-USA)	—	6,850	—	6,750
2. Ammann (USA)	–	178	—	106
Subtotal	—	7,028	—	6,856
Other[d]				
1. Austrian (South Africa) (3 trials)	4,000	—	8,000	—
Subtotal	4,000	—	8,000	—
SUBTOTAL	11,647	7,120	17,541	6,856
TOTAL	18,767		24,397	

[a] These studies were sponsored by Merck Sharp and Dohme (MSD).
[b] This study was cosponsored by Merck Sharp and Dohme and the Department of Public Health, Papua, New Guinea.
[c] These studies were sponsored at least part by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).
[d] These studies were sponsored by the Chamber of Mines of South Africa.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal investigators of included studies, 1979

pensive. For this reason, some investigators, namely, Austrian and Merck Sharp and Dohme, conducted clinical trials of pneumococcal vaccine among foreign populations with high pneumococcal pneumonia incidence rates (e. g., South African gold miners, among whom the estimated incidence is at least 90 cases per 1,000 persons per annum). The numbers of foreign and domestic subjects involved in premarketing clinical trials and other studies of pneumococcal vaccine are shown in table 10.

The wisdom of basing evaluations of pharmaceutical and biological products intended for use in the United States on the results of tests conducted among foreign populations has been debated for several years. On the one hand, testing among foreign populations may be necessary, because, as in the case of pneumococcal disease, the incidence of a targeted medical problem in the United States is either unknown or too low to permit accurate assessment of a product's clinical efficacy and safety. On the other hand, data generated in foreign-based testing may be an inadequate basis on which to evaluate the safety of a product to be used in the United States for two reasons:

1. Results obtained in safety tests conducted among subjects in foreign countries, because of culturally influenced perceptual differences and living condition variations, for example, might differ significantly from results that are yielded in similar studies among subjects who reside in the United States.
2. Foreign trials might not include or permit followup observation of vaccinees for the assessment of delayed onset or rare reactions.

Foreign trials per se are not always necessarily inadequate. As is true for clinical trials conducted in this country, each foreign investigation deserves to be evaluated independent] y.

Without premarketing clinical trials of the vaccine in South Africa, there probably would be no licensed pneumococcal vaccine in the United States today. BOB would have

Table 10.—Number of Foreign and Domestic Subjects Involved in Premarketing Clinical Trials and Studies of Pneumococcal Vaccine

	Number of subjects					
	Clinical safety and efficacy trials[a]		Epidemiologic studies[b]		Immunogenicity studies[c]	
Sponsor	Foreign	Domestic	Foreign	Domestic	Foreign	Domestic
Industry	7,647	92	299	0	4,130	274
Government	0	7,028	0	329	0	4,055[c]
Academe	0	0	0	12,198	0	0
Other	4,000	0	177		11	0
Subtotal	11,647	7,120	476	12,527	4,141	4,329
Total	18,767		13,003		8,470	

[a]Numbers include vaccinees only.
[b]Numbers refer to cases, not subjects.
[c]Some of these data are still being analyzed by the investigator.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, Merck Sharp and Dohme, the National Institute of Allergy and Infectious Diseases, and principal investigators of included studies, 1979.

had no evidence of the vaccine's clinical efficacy, because studies of polyvalent pneumococcal vaccines conducted in the United States and New Guinea did not generate statistically significant efficacy results. Austrian's study at the San Francisco Kaiser Permanence Medical Center was rigorously designed, but not helpful in documenting efficacy of pneumococcal vaccine because of the very low incidence of pneumococcal respiratory diseases in both the experimental and control populations. Similarly, Riley's study in New Guinea was not helpful to BOB in assessing the efficacy of pneumococcal vaccine, because investigators in this study measured the reduction in the incidence of lower respiratory tract infection (LRTI), not type-specific pneumococcal disease.

To evaluate the clinical efficacy of pneumococcal vaccine, BOB had to rely heavily on data from five South African trials in which the primary emphasis was on the evaluation of vaccine efficacy. While BOB was able to rely on these trials' efficacy data, it had to view clinical safety data from these trials of pneumococcal vaccine more critically.

There would seem to be two particular limitations to the usefulness of foreign data regarding the safety of pneumococcal vaccine. First, unlike efficacy data, safety data are generated largely on the basis of vaccinees' subjective responses; the extrapolation of foreign safety data to U.S. populations, therefore, may not be valid. All 5,701 subjects involved in the South African studies (30 percent of the total) were young black male gold miners, mostly from Malawi and Mozambique. These foreign subjects very possibly might have perceived adverse reactions to the vaccine differently, or been less able or willing to complain about or report adverse reactions, than vaccine recipients in the United States. Investigators' ability to assess the rate of adverse reactions to pneumococcal vaccine also may have been hindered by the prevalence among these foreign subjects of mimicking symptoms that were not caused by the vaccine. Fever, for example, is a known possible adverse reaction to pneumococcal vaccine, and many vaccinees in South African clinical trials had fevers from infections such as malaria. Even if cases of malaria were evenly distributed between experimental and control groups, investigators' ability to establish a causal relationship between pneumococcal vaccination and fever undoubtedly was hampered.

The second problem with basing an evaluation of pneumococcal vaccine's safety on data from foreign trials is that the methods researchers in some foreign studies used to solicit reports of adverse reactions may not have permitted accurate or comprehensive assessment of such reactions. Researchers in Merck's two South African studies, No. 315 and No. 315A, used physicians, nurses, and other trained aides to observe vaccinees for

adverse reactions, but vaccinees were observed for a period of only 3 days subsequent to vaccination (Smit, 1977). No attempt to monitor vaccine recipients for delayed-onset adverse reactions was made; however, vaccinees had access to medical care throughout their participation in the study and could voluntarily report serious adverse reactions. In Riley's study in New Guinea, only 133 of 5,946 vaccinated subjects were monitored for adverse reactions (Riley, 1977).

That BOB was quite aware of the limitations of using foreign trial data to evaluate the safety of pneumococcal vaccine is evidenced by the following response to an early draft of this OTA report from one BOB official (Parkman, 1979):

> It is true that common local and febrile reactions may have been more difficult to assess under the circumstances of the South African and New Guinea trials; this was understood at the time these studies were undertaken. The primary emphasis of these trials was on the assessment of effectiveness.
>
> Certainly, however, the opportunity to also gain information on adverse reactions seemed worth the effort. In clinical trials of this sort, it is common to have a period of intensive observation when reactions are most likely to occur, and a more general surveillance directed toward followup of any unusual events which are reported to the investigators or which are reported to those physicians caring for study participants. Thus, severe reactions at the inoculation site or severe systemic reactions of frequent occurrence would have been detected in the 3-day observation period, since previous experience with these and other earlier pneumococcus vaccines indicated this to be the period in which local and systemic reactions were most likely to occur.

One possible problem with heavy reliance on short observation periods in foreign investigations is that researchers may lack the opportunity or willingness to conduct a follow-up surveillance of adverse reactions, especially after a trial has produced adequate efficacy data.

In general, studies of polyvalent pneumococcal vaccines conducted in the United States generated higher reported incidence rates of vaccine-related side effects than did those conducted in foreign countries. (See table 7.) In total, 7,120 (38 percent) of the 18,767 subjects vaccinated in safety studies were U.S. residents. (See table 10.) If BOB's assessment of the safety of pneumococcal vaccine had been based solely on data from studies involving these 7,120 domestic subjects, then the question would have arisen: Is this an adequate sample on which to base an evaluation of the safety of a product that will be administered to millions of Americans? The answer would lie in the degree of safety assessment believed necessary. Most acute, commonly occurring, local and systemic reactions probably could have been detected in a sample this size. Less common adverse reactions and any reactions with delayed onset, however, most likely would have escaped detection.

Lack of Vaccine Testing Among High Risk Populations

One should not assume from the FDA-approved pneumococcal vaccine "Indications" statement (see figure 10) that, prior to Government licensure, the new vaccine was tested for safety or efficacy among high risk individuals with the medical problems (e.g., diabetes, heart disease, or lung disease) that are listed as indications for vaccine use. No premarketing clinical trial specifically assessed pneumococcal vaccine's efficacy or safety among groups of individuals with one or more of the chronic medical problems listed as official indications for vaccine use. Most premarketing clinical trials of this vaccine were conducted among individuals in healthy populations, who, though possibly at high risk of encountering pneumococcal disease, were not necessarily at high risk of becoming

seriously ill or dying from such disease. One study, however, did assess the clinical efficacy of a pneumococcal vaccine in children with sickle-cell disease (Ammann, 1977).

Rather than data from clinical trials, the primary basis for FDA's approval of the "Indications" statement on pneumococcal vaccine's label were data from a study of mortality rates among 529 patients with bacteremic pneumococcal pneumonia. In this study, conducted at a New York hospital between 1952 and 1962, Austrian and Jerome Gold found that the incidence of mortality caused by pneumococcal pneumonia or bacterernia was higher in patients with certain types of chronic medical problems than in patients without such problems (Austrian, 1964). They also found higher mortality rates from these diseases among those over the age of 50 than among those who were younger. In another study of 325 adult subjects with pneumococcal pneumonia, similar mortality patterns were demonstrated (Mufson, 1974).

Like clinical trials, most immunogenicity studies of pneumococcal vaccine were conducted among healthy subjects. Prior to Licensure, the immunogenicity of this vaccine in specialized populations most likely to contract or die from pneumococcal disease was investigated in only two studies. In one study among a small number of subjects, it was demonstrated that the vaccine could produce good antibody responses in the elderly (Bentley, 1974). Another study demonstrated that the vaccine was immunogenic among children with sickle-cell anemia and children with inadequate spleen function (Ammann, 1977).

One reason for the lack of new vaccine testing in premarketing clinical trials among high risk individuals is that rigorous adherence to randomized controlled clinical trial standards frequently may pose ethical dilemmas for investigators. These standards require that all test subjects be assigned randomly to either an experimental group, which receives the product being tested, or a control group, which does not. Investigators must withhold an experimental vaccine (which by this time in clinical testing must already have demonstrated some degree of efficacy) from individuals at high risk of contracting and possibly dying from the potentially preventable disease, and must administer the vaccine to other high risk individuals who may be particularly susceptible to serious vaccine-induced adverse reactions. To avoid the ethical dilemma posed by withholding an experimental vaccine from someone who would likely benefit from vaccination or giving such a vaccine to someone who is at high risk of experiencing a severe adverse reaction, clinical investigators tend most often to conduct trials among healthy populations.

Economic constraints associated with conducting premarketing clinical trials also may preclude extensive testing in high risk individuals. Testing vaccines in rigorous clinical trials among specialized high risk populations may consume substantial investments in research resources and time. Sponsors of such clinical investigations sometimes pay for the medical care rendered to participating patients. Furthermore, finding concentrated high risk populations that are suitable for clinical vaccine testing is sometimes more difficult than identifying a suitable population of healthy volunteers.

At present, the requirement that a new vaccine be tested in high risk populations is determined by BOB and the vaccine manufacturer. Whether or not BOB and a vaccine manufacturer believe that clinical trial data from high risk populations are needed depends at least in part on the availability of safety and efficacy data from other types of studies. According to one BOB official, further testing of pneumococcal vaccine among individuals at high risk was not felt to be necessary (Parkman, 1978):

> This [the assessment of the pneurnococcal vaccine in clinical trials involving high risk individuals] was not a major consideration in the minds of those who planned the trials or those who evaluated them because of the general experience with inactivated vaccine in immunologically mature children and normal adults as well as in persons in these groups with a variety of conditions (e.g., diabetes, heart disease, lung disease) which indicates that they all behave in a similar fashion with regard to adverse reactions and immunologic response patterns.
>
> Thus it would not seem an economical use of resources to set up studies in which groups of, say, cardiac patients were evaluated. The exceptions to this generalization are those patient groups who, for whatever reason, are immunosuppressed. Here the consideration is efficacy, not safety. A prime example here would include patients with splenic dysfunction, this group was studied by Ammann . . .
>
> All in all, the consensus of the various groups who evaluated the data at the time of licensure both within the Bureau and among experts outside the Government was that the available information was adequate.

For- the reasons cited, FDA established indications for use of pneumococcal vaccine based primarily on a person's risk of contracting or dying from pneumococcal pneumonia, basically assuming—unless and until proved otherwise—that the vaccine would work in high risk individuals. The net result of not involving high risk persons in premarketing clinical trials, however, is this: The safety and efficacy of pneumococcal vaccine never was thoroughly evaluated prior to licensure among persons for whom the vaccine may provide the greatest benefit.

The potential implications of requiring premarketing clinical testing of a vaccine specifically among high risk individuals are unclear. To permit clinical trials to be conducted among high risk individuals, bioethical research standards might have to be modified. Furthermore, the added expense of such clinical testing, if required, might undermine vaccine manufacturers' willingness to engage in vaccine research and development. One implication of requiring such c1inical testing, however, is certain: A new vaccine's safety and efficacy among high risk individuals would be better understood.