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A CASE STUDY: FINANCING THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE

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A glance at the record makes one point indisputable: new vaccine development in the U.S.A. has been second to none, and we must have been doing many things right.

Maurice R. Hilleman, Ph. D., D. SC.
Director, Merck Institute for Therapeutic Research
November 14, 1976[1]

Never take your vaccine supply system for granted,

Harry M. Meyer, Jr., M.D.
Director, Bureau of Biologics
November 13, 1976[1]

BACKGROUND AND INTRODUCTION

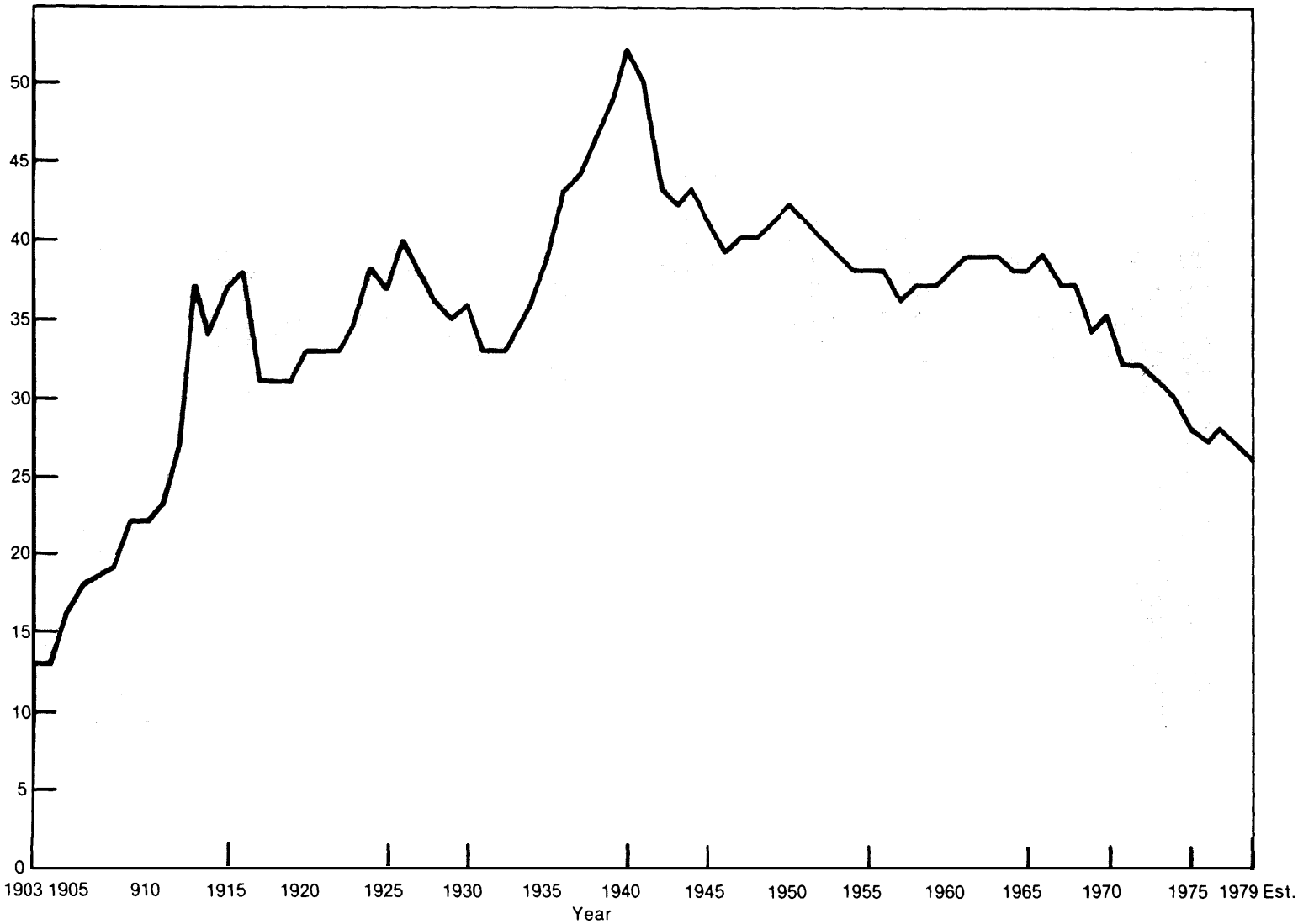
During the past few years, concern has been expressed about the decline in the number of American pharmaceutical companies engaged in the research, development, and production of vaccines. Some authorities have speculated that the capacity of the pharmaceutical industry to develop and produce needed vaccines has dwindled to the point that increases in Federal funding for vaccine research and development—and, possibly, even Government production of certain vaccines that the industry drops—soon may be necessary (Krugman, 197'7).

Since the early 1940's, there has been a definite decline in the number of licensed vaccine manufacturers and licensed vaccine products in this country. (See figures 3 and 4.) Furthermore, the number of licensed vaccine products per licensed manufacturer also has declined. (See figure 5.) Possible reasons for the general decline since the 1940's, including the discovery and widespread use of antibiotics, are discussed briefly in appendix 2.1.

No full investigation of the causes of the decline in the number of vaccine manufacturers or of its potential effect on vaccine research, development, and production in this country has been made. Similarly, there has been no comprehensive assessment of the net effect of various Federal vaccine policies and regulations on industry behavior. The effect of the following Federal actions on the pharmaceutical industry's willingness to develop

'Statement presented at the National Immunization Conference sponsored by the National Institutes of Health, Bethesda, Md., Nov. 13 and **14, 1976,**

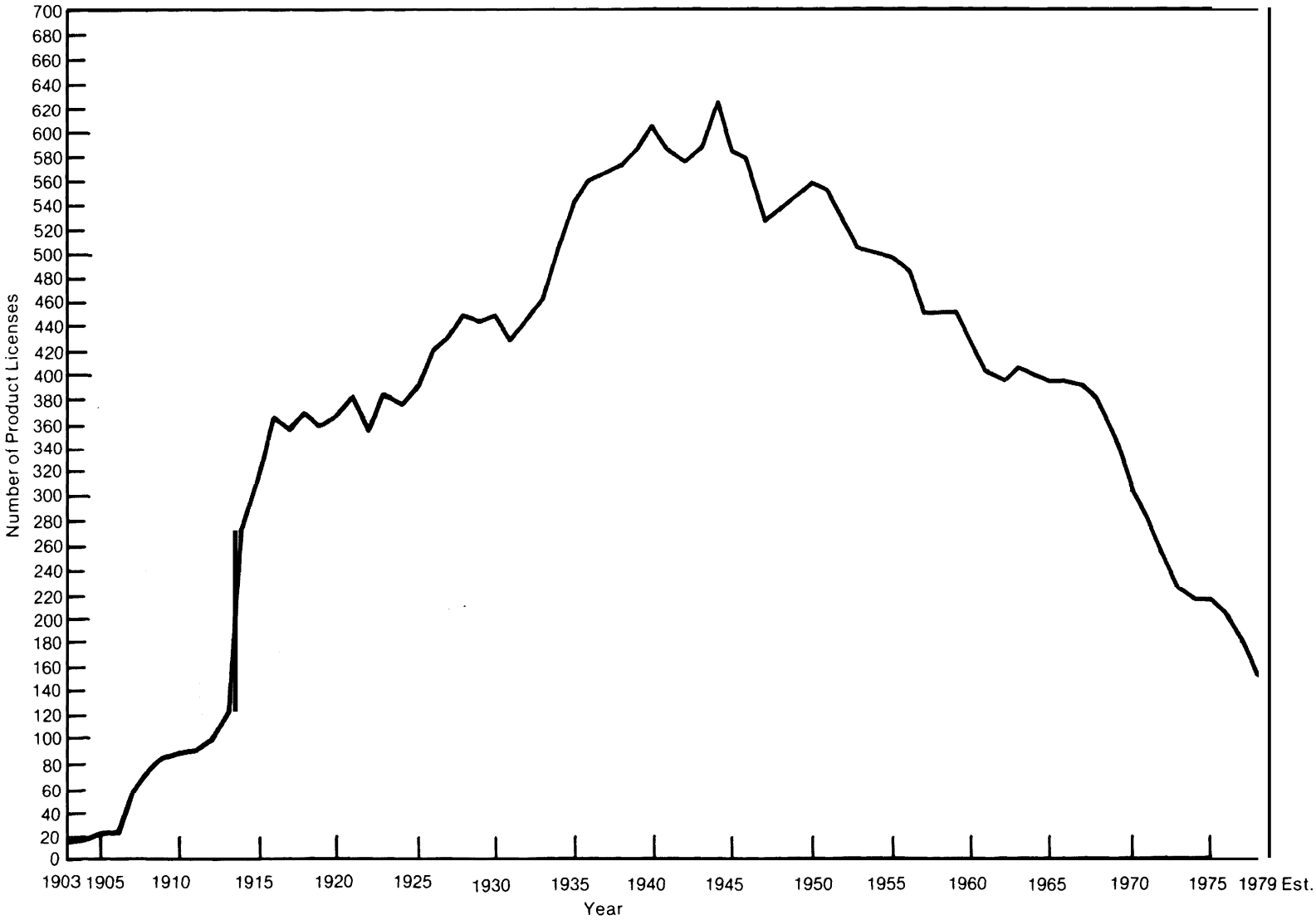
Figure 3.—Total Number of Vaccine Manufacturing Establishments Licensed in the United States by Year (1903-79)[1]



The number of licenses shown on this graph represents the net number of active vaccine *establishment* licenses for each year. Totals for each year were calculated by tallying a running total of the number of vaccine *establishment* licenses issued over time and subtracting the number of vaccine *establishment* licenses revoked over time.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979.

Figure 4.—Total Number of Vaccine Products Licensed in the United States by Year (1903-79)[1]



[1]The number of licenses shown on this graph represents the net number of active vaccine *product* licenses for each year. Totals for each year were calculated by tallying a running total of the number of vaccine *product* licenses issued over time and subtracting the number of vaccine *product* licenses revoked over time.

SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979

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and produce vaccines, therefore, is unknown: NIAID's funding of certain types of vaccine research and development, BOB's evaluating vaccine safety and efficacy, CDC's purchasing of vaccines for public immunization programs, and HEW's handling of vaccine liability and compensation issues.

In order to assess the impact of Government actions on industry behavior, it is important to know what general factors influence individual pharmaceutical manufacturers' decisions to enter, stay in, expand within, or withdraw from the vaccine business. From selected readings and from interviews with representatives of the pharmaceutical industry and certain government agencies, the following influences on individual pharmaceutical manufacturers' decisions to conduct vaccine research, development, and production can be identified:

1. The size of the potential market for a given vaccine product.
2. The availability of company personnel and facilities needed to engage in vaccine research, development, and production.
3. The cost and complexity of complying with Federal regulations concerning vaccine safety and efficacy.
4. The manufacturer's ability to predict potential costs of liability for harm produced through the use of vaccines.
5. The availability of Government financing for vaccine research and development, and possibly, production.
6. The manufacturer's ability to establish adequate selling prices for vaccine products.
7. The public need for a given vaccine and the extent to which this need is being met by other manufacturers.

Since 1968, the number of licensed manufacturing establishments that produce vaccines in this country has droppped about 50 percent—from about 37 to 18. The number of licensed vaccine products has dropped about 60 percent—from 385 to around 150. The impact of this recent decline on the U.S. pharmaceutical industry's ability to develop and produce supplies of vaccines commensurate with public need is unknown. The apparently diminishing commitment—and possibly capacity—of the American pharmaceutical industry to research, develop, and produce vaccines, however, may be reaching levels of real concern.

At the present time, there are 26 licensed vaccine establishments. Only 18 establishments actually produce vaccines for sale in the United States. Eight of the 18 establishments are American pharmaceutical companies. These eight companies hold 100 (70 percent) of the 143 vaccine product licenses in this country; foreign-based establishments hold 24 (17 percent); and two State governments and one American university hold the remaining 19 (13 percent). (See table 1.)

The 143 vaccine products currently licensed in the United States can be assigned on the basis of product content to about 51 different categories. Altogether, these products are intended to provide immunity against about 23 different types of infections. (See table 2.) For 20 (40 percent) of the 51 currently licensed types of products, there is only one manufacturer licensed in the United States. (See table 3.)

Eight American pharmaceutical companies collectively hold 100 current product licenses[2] for 51 different types of vaccines. Fifty-five of these licenses are being used to

[2]In table 4, 10 products are subsumed under one license (polyvalent bacterial vaccines with "no U.S. standard of potency").

Table 1 .–Vaccine Manufacturing Establishments Currently Licensed in the United States (1979)

Category and name of establishment	Number of product licenses
American pharmaceutical companies	
1. Connaught Laboratories, Inc..	15
2. Cutter Laboratories (includes Hollister-Stier)	3
3. Delmont Laboratories, Inc..	1
4. Eli Lilly and Company	9
5. Lederle Laboratories.	20
6. Merck Sharp and Dohme.	12
7. Parke, Davis and Company.	18
8. Wyeth Laboratories, Inc....	12
Subtotal	100 (70%)
Foreign institutions	
1. Connaught Laboratories, Ltd.	5
2. Glaxo Laboratories, Ltd.	1
3. institute Sieroterapico Vaccinogeno Tuscano Sclavo	10
4. Pfizer, Ltd.	4
5. Recherche et Industrie Therapeutiques S.A.	1
6. Swiss Serumand Vaccine Institute Berne	2
7. Wellcome Foundation, Ltd. Wellcome Research Laboratories	1
Subtotal	24 (17%)
State governments	
1. Bureau of Laboratories, Michigan Department of Public Health	9
2. Massachusetts Public Health Biologic Laboratories	9
Subtotal	18 (13%)
American universities	
1. University of Illinois	1
Subtotal	(< 1 %)
Grand total	143(1OO%)

SOURCE OTA's Interpretation of data provided by the Bureau of Biologics. 1979

Table 2.—Diseases Against Which There Are Currently Licensed Immunizing Agents in the United States (1979)

General population (7 diseases)	Special populations (16 diseases)
Diphtheria	Adenovirus
Pertussis	Anthrax
Polio	BCG
Measles	Cholera
Mumps	Gas gangrene
Rubella	Influenza
Tetanus	Meningococcal diseases
	Plague
	Pneumococcal pneumonia
	Rabies
	Rocky Mountain Spotted Fever
	Smallpox
	Staphylococcal disease
	Typhoid
	Typhus
	Yellow Fever

SOURCE OTA's interpretation of data provided by the Bureau of Biologics 1979

Table 3.—Vaccine Products With Only One Manufacturing Establishment Currently Licensed in the United States (1979)

	Type of product	Number of establishments holding product license: American pharmaceutical companies	Foreign-based institutions	American universities	State governments
1	Adenovirus and influenza virus vaccines combined alumlnum phosphate adsorbed	1			
2	Adenovirus vaccine	1			
3	Anthrax vaccine adsorbed				1
4	Diphtheria tetanus toxoids, pertussis vaccine adsorbed, poliomyelitis vaccine	1			
5	Diphtheria, tetanus toxoids, pertussis poliomyelitis vaccines adsorbed	1			
6	Gas gangrene polyvalent antitoxin	1			
7	Measles and mumps virus vaccines, live	1			
8	Measles and rubella virus vaccine, live	1			
9	Measles-smallpox vaccine. live.	1			
10	Measles. mumps, and rubella virus vaccine, live	1			
11	Mumps virus vaccine, live	1			
12	Pertussis vaccine adsorbed	1			
13	Plague vaccine . . .	1			
14	Poliomyelitis vaccine adsorbed	1			
15	Polyvalent bacterial antigens with "no U.S. standard of potency"	1			
16,	Polyvalent bacterial vaccines with "no U.S. standard of potency" . . .	1			
17	Rabies vaccine	1			
18	Rocky Mountain Spotted Fever vaccine	1			
19	Rubella and mumps virus vaccine, live . . .	1			
20.	Yellow Fever vaccine ., ...	1			
	Totals.	19	—	—	1

SOURCE OTA s interpretation of data provided by the Bureau of Biologics. 1979.

market 31 types of products. Twenty of the 51 currently licensed types of vaccines have no producer. Eighteen have only one producer, 7 have two producers, 2 have three producers, and 4 have four or more producers. (See table 4.) If technological or marketing problems were to cause a shutdown of production, it is conceivable that certain types of vaccine products might become unavailable—at least for a period of time. (See appendix 2.2.)

New types of products have been introduced at a rate of three to seven products every 5 years since 1940. (See table 5.) American pharmaceutical companies have introduced about 42 (82 percent) of the 51 currently available types of vaccines. (See appendix 2.3.)

Several factors may have contributed to the recent decline in the number of licensed vaccine establishments and products. First, in 1972, the Licensing Branch of the Food and Drug Administration's (FDA) Bureau of Biologics (BOB) launched a concerted effort to remove inactive vaccine product licenses. Second, rather than comply with new standards for product safety and efficacy issued by FDA in 1972, many licensed establishments may have opted to cease vaccine production. Third, in recent years, manufacturers have been faced with a static vaccine market and increasing production costs. Finally, vaccine manufacturers' liability for the infrequently occurring injury produced by vaccination has been broadened.

The focus in this chapter is on issues pertaining to the manner in which Federal Government policies influence pharmaceutical manufacturers' decisions to undertake vaccine

Table 4.—Commercial Availability in the United States of Vaccine Products Manufactured by American Pharmaceutical Companies (1979)[a]

Type of product	Number of American corporations licensed to market the product in the United States	Number of American corporations actually market ing the product in the United States	Number of foreign establishments licensed to market the product in the United States
1. Adenovirus and influenza virus vaccines combined aluminum phosphate adsorbed	1	None	None
2. Adenovirus vaccine	1	None	None
3. Antirabies serum	1	1	1
4. Anthrax vaccine adsorbed[b]	None	None	None
5. BCG vaccinec	None	None	2
6. Cholera vaccine	4	2	1
7. Diphtheria antitoxind	1	1	1
8. Diphtheria and tetanus toxoids	2	None	None
9. Diphtheria and tetanus toxoids	2	None	None
10. Diphtheria and tetanus toxoids and pertussis vaccine adsorbedd	6	4	1
11. Diphtheria and tetanus toxoids adsorbedd	4	3	1
12. Diphtheria toxoid[b]	3	None	1
13. Diphtheria toxoid adsorbed[b]	2	None	1
14. Diphtheria, tetanus toxoids, pertussis vaccine adsorbed, poliomyelitis vaccine	1	None	None
15. Diphtheria, tetanus toxoids and pertussis, poliomyelitis vaccines, adsorbed	1	None	None
16. Gas gangrene polyvalent antitoxin	1	None	None
17. Influenza virus vaccine	5	4	None
18. Measles and mumps virus vaccine, live	1	1	None
19. Measles and rubella virus vaccine, live	1	1	None
20. Measles virus vaccine, live, attenuated	2	2	None
21. Measles-smallpox vaccine, live	1	None	None
22. Measles, mumps, and rubella virus vaccine, live	1	1	None
23. Meningococcal polysaccharide vaccine, Group A	2	2	None
24. Meningococcal polysaccharide vaccine, Group C	2	2	None
25. Meningococcal polysaccharide vaccine, Groups A and C combined	2	2	None
26. Mumps virus vaccine, live	1	1	None
27. Pertussis vaccine	4	1	None
28. Pertussis vaccine adsorbedb	1	None	None
29. Plague vaccine	1	1	None
30. Pneumococcal vaccine, polyvalent	2	2	None
31. Poliomyelitis vaccine	2	None	1
32. Poliomyelitis vaccine adsorbed	1	None	None
33. Poliovirus vaccine, live oral trivalent	1	1	1
34. Poliovirus vaccine, live oral, Type 1	1	None	1
35. Poliovirus vaccine, live oral, Type 2	1	None	1

Table 4.—Commercial Availability in the United States of Vaccine Products Manufactured by American Pharmaceutical Companies (1979)'–cont.

Type of product	Number of American corporations licensed to market the product in the United States	Number of American corporations actually marketing the product in the United States	Number of foreign establishments licensed to market the product in the United States
36. Poliovirus vaccine, live oral, Type 3 ..	1	None	1
37. Polyvalent bacterial antigens with "no U.S. standard of potency"	1	1	None
38. Polyvalent bacterial vaccines with" no U.S. standard of potency"	1	1	None
39. Rabies vaccine[f]	1	1	None
40. Rocky Mountain Spotted Fever vaccine	1	None	None
41. Rubella and mumps virus vaccine, live	1	1	None
42. Rubella virus vaccine, live	1	1	2
43. Smallpox vaccine[b]	3	2	1
44. Staphylococcus toxoid ...	1	1	1
45. Tetanus and diphtheria toxoids adsorbed (for adult use)[b]	5	4	None
46. Tetanus toxoid[b]	7	3	2
47. Tetanus antitoxin	3	None	2
48. Tetanus toxoid adsorbed[d]	6	5	2
49. Typhoid vaccine	2	1	None
50. Typhus vaccine[e]	3	1	None
51. Yellow Fever vaccine	1	1	None
Totals	100	55	24

[a]Includes 2 serums and 11 antitoxin products.
[b]Product license held also by one State government laboratory.
[c]Product license held by one American university.
[d]Product licenses held also by 2 State government laboratories.
[e]One of the two American pharmaceutical companies licensed to market this measles vaccine in the United States plans to remove the product from interstate commerce in 1980.
[f]The one American pharmaceutical company that currently markets rabies vaccine plans to stop marketing it if another company is licensed for this product.
SOURCE: OTA's interpretation of data provided by the Bureau of Biologics and the eight American vaccine manufacturers, 1979.

Table 5.— Number of New or Improved Types of Currently Licensed Vaccine Products Introduced in the United States in 5-Year Intervals Since 1940a

5-year time interval	Number of new or improved types of vaccine products introduced
1975-1979	4
1970-1974	6
1965-1969	3
1960-1964	7
1955-1959	4
1950-1954	6
1945-1949	6
1940-1944	3
Before 1940	10
Total	49

[a]Only 49 of the currently licensed 51 types of licensed products are included. Polyvalent bacterial antigens and polyvalent bacterial vaccines with "no U.S. standard of potency" are excluded.
SOURCE: OTA's interpretation of data provided by the Bureau of Biologics, 1979.

research, development, and production activities. Specifically examined is NIAID's role vis-a-vis private industry in financing the research and development of a polyvalent pneumococcal polysaccharide vaccine. Findings from this case study and issues related to the development and overall impact of Federal Government policies on private sector vaccine research, development, and production activities, are presented in chapter 6. Possible options for congressional action are presented in chapter 7.

EARLY PNEUMOCOCCAL VACCINE RESEARCH AND DEVELOPMENT (1881-1966)[3]

Pneumococcal vaccine research and development efforts prior to 1967 were uncoordinated, poorly funded, and not highly visible. Like other basic scientists, early pneumococcal researchers, mostly in academe and private industry, worked with no single leader or coordinated research plan. In the late 1800's and early 1900's, communication among pneumococcal researchers was limited to periodic publications in scientific and clinical journals and infrequent personal exchanges. Research funds, although provided by a variety of sources, were generally scarce.

In the late 1940's, based upon the clinical safety, efficacy, and immunogenicity data generated by such researchers as Lloyd Felton, Colin M. MacLeod, Paul Kaufman, and Michael Heidelberger, E. R. Squibb and Sons developed and marketed two 6-valent pneumococcal capsular polysaccharide vaccines. One vaccine, formulated for use in adults, contained polysaccharide Types 1, 2, 3, 5, and 8; the other vaccine, intended for use in children, contained Types 1, 4, 6, 14, 18, and 19.

Neither of Squibb's vaccines ever gained widespread acceptance. Physicians in the early 1950's chose to rely on newly introduced antimicrobial agents (penicillin, sulfonamides, chlortetracycline, and chloramphenicol) to treat bacterial pneumonia, rather than to help prevent this disease through immunization. In 1954, therefore, Squibb terminated its production of pneumococcal vaccine. The Biologics Control Agency (then the Laboratory of Biologics Control of the National Microbiologic Institute, NIH) withdrew without prejudice Squibb's license to produce these vaccines, and the company subsequently abandoned all of its pneumococcal vaccine research and development programs.

After this, with increasing reliance on antibiotic treatment therapy, perceptions of the need for the development of a pneumococcal polysaccharide vaccine generally diminished until Robert Austrian and Jerome Gold produced data between 1952 and 1962, showing that, despite antibiotic treatment, the mortality rate for bacteremic pneumococcal pneumonia was still high (Austrian, Gold, 1964). In their study at Kings County Hospital in Brooklyn, N. Y., these researchers found that 10 types of pneumococci accounted for at least 70 percent of pneumococcal pneumonia cases. Of patients treated for bacteremic pneumococcal pneumonia with penicillin or other antibiotics, 17 percent died. Among patients over 50 years of age, the mortality rate was 28 percent; and among individuals with complicating illnesses such as heart disease, stroke, and pulmonary emphysema, the mortality rate was 30 percent.

In addition, other investigators found that the emergence of antibiotic resistant strains of pneumococci was becoming a significant problem in the treatment of pneumococcal diseases (Dixon, 1967). These findings sparked renewed interest in the development of a pneumococcal vaccine.

[3]For a more extensive review of private sector pneumococcal vaccine research and development efforts prior to 1967, see app. I .1,

FEDERAL GOVERNMENT PARTICIPATION IN THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE (1967-79)

Federal Government participation in the research and development of a polyvalent pneumococcal polysaccharide vaccine dates from 1967. At the strong and insistent urging of Robert Austrian, the National Institute of Allergy and Infectious Diseases (NIAID), one of the 11 Institutes at the National Institutes of Health (NIH), in 1967, committed itself to providing substantial Federal funds for the research and development of a pneumococcal polysaccharide vaccine.

There were three reasons underlying NIAID's decision, based on the recommendation of its Vaccine Development Committee (VDC), to provide funding for research and development of a pneumococcal vaccine (Davis, 1967):

1. For some years prior to 1967, NIAID had been considering initiating a goal-oriented, contract-supported program to develop bacterial vaccines.
2. The work of Austrian and other researchers demonstrated that pneumococcal diseases had not been conquered by antibiotics and that the development of a safe and effective vaccine against these diseases was technically feasible.
3. After contacting the Pharmaceutical Manufacturers Association (PMA), NIAID concluded that no pharmaceutical company was interested at the time in developing a pneumococcal vaccine on its own.

The Federal Government traditionally has financed a significant amount of basic and epidemiologic research on vaccines through the provision of grants to basic researchers.[4] Some basic and epidemiologic research also has been financed by the pharmaceutical industry. Prior to 1967, the Federal Government had funded vaccine product development and clinical testing,[5] but the primary source of funding for this was the private sector, specifically, individual pharmaceutical companies expecting to develop a marketable product.

On the basis of the size of NIAID's financial commitment to pneumococcal vaccine in 1967, it would appear that this agency perceived a need for greater Federal involvement in financing vaccine research and development than had been called for in the past. Between 1968 and 1976, NIAID spent an estimated $6.5 million for basic research on the pneumococcus and for development and testing of pneumococcal vaccines. Of this amount, $2. o million was allocated to basic research on the pneumococcus and epidemiologic research of pneumococcal diseases, and $4.5 million was devoted to the development and testing of pneumococcal vaccines.

The objectives of this NIAID-sponsored research were these (Horton, 1973):

1. To assess the predominant types of pneumococci causing illness and to determine the incidence of pneumococcal disease among certain high risk populations;
2. To develop serological procedures to enhance the diagnosis of pneumococcal disease and to facilitate the collection of essential data that characterize the antigenic potential of pneumococcal vaccines;
3. To evaluate pneumococcal (monovalent and polyvalent) vaccines in clinical trials for clinical efficacy, safety, and immunogenicity; and

[4]NIAID continues today to provide substantial funds for basic, epidemiologic, and clinical research. Most researchers who receive Federal funds work in academe, although some work in private industry.

[5]For example, it was heavily involved in field testing of polio, measles, and rubella vaccines. In the 1960's, NIAID's Vaccine Development Branch, and in the 1940's, the Commission on Influenza of the Armed Forces supported substantial product development and clinical testing activities.

4. To stimulate the commercial production and eventual licensure of a safe, highly purified, polyvalent pneumococcal vaccine.

NIAID-funded research began in 1968. That year NIAID contracted with Austrian and other researchers in academe and private medical practice to conduct epidemiologic studies to determine the incidence of pneumococcal disease and to establish the distribution of the most common serotypes of pneumococci producing these diseases. NIAID also contracted with Austrian at the University of Pennsylvania and later with Gerald Schiffman at the State University of New York at Brooklyn to develop serological methods of diagnosing pneumococcal disease and measuring antibody responses.

In addition to funding basic research, NIAID awarded a contract to Eli Lilly and Company, a pharmaceutical manufacturer, to develop an experimental polyvalent pneumococcal polysaccharide vaccine for use in clinical trials. In the early 1970's, NIAID also contracted with clinical investigators in academe and private practice to conduct U.S. clinical trials of pneumococcal vaccine. For two of the studies, one at Kaiser Permanence Medical Center in San Francisco, Calif., and another at the Dorothea Dix Hospital in Raleigh, N. C., Austrian served as principal investigator. ' In another study, which was partially funded by NIAID, the clinical efficacy, safety, and immunogenicity of an 8-valent pneumococcal vaccine were evaluated in children with sickle-cell disease and hyposplenic function (Ammann, 1977).

Since 1974, NIAID has been collaborating in at least 30 clinical studies involving the use of polyvalent pneumococcal vaccine in special populations at high risk, such as those with sickle-cell disease or inadequate splenic function. NIAID does not provide direct funding for such studies, but it does provide both staff time for coordination of study activities and use of contract laboratory facilities. In addition, it facilitates researchers' access to manufacturer-supplied vaccines.

INDUSTRY PARTICIPATION IN THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE (1967-79)

Following the termination of Squibb's pneumococcal vaccine research, development, and production programs in the 1950's, little additional work on pneumococcal polysaccharide vaccines was done by the pharmaceutical industry until 1968, when Eli Lilly began preparing vaccines under contract from NIAID.

Prior to accepting the NIAID contract, Lilly had not been working independently on the development of a pneumococcal vaccine, but was involved in the manufacture of other vaccines and was attempting to develop a vaccine to prevent common respiratory infections. Thus, Lilly's decision to undertake the task of developing and producing experimental pneumococcal polysaccharide vaccine may have been influenced by the company's involvement in other vaccine-related activities. This decision, however, also may have been influenced by the availability of Federal funds for pneumococcal vaccine development. Lilly had also accepted NIAID funds in the 1960's to develop rubella vaccine.

Lilly eventually produced thousands of doses of monovalent and polyvalent vaccines of purified polysaccharide Types 1-9, 12, 14, 18, 19, 23, and 25. According to some Government officials, though, Lilly's pneumococcal vaccine researchers encountered

'NIAID-sponsored studies, along with other clinical trials and studies designed to assess the safety and efficacy of experimental polyvalent pneumococcal vaccines, are described in ch. 3 and in app. 3.6.

substantial problems during the first 18 months of their contract (U.S. Ex. Br., NIAID, 1970).

As Lilly was producing experimental pneumococcal vaccines, company officials were considering dropping the bulk of Lilly's vaccine research, development, and production programs. Apparently, the company's vaccine-related activities were not as profitable as its activites in other product areas. Specific problems related to vaccines included these (Johnson, 1978):

1. The vaccine market did not appear to be growing. Vaccine use at the time was largely aimed at preventing certain childhood diseases, and at least four producers competed for shares of the existing vaccine market. Because the U.S. birth rate was declining, the childhood disease vaccine market was expected to decl inc.
2. Vaccine research was expensive and required substantial investments in technology and human resources. Prescription drug products manufactured in tablet or capsule form were often less expensive to produce than vaccines and usually generated higher profits.
3. Documenting the efficacy of a vaccine in the United States was difficult and expensive. This was especially true for pneumococcal vaccine, a product designed to treat a disease whose incidence even today remains difficult to assess and for which accurate diagnostic techniques can be expensive and difficult to perform.[7]
4. Proving the quality of each batch of vaccines manufactured, as required by Federal regulations, was expensive. Samples of each batch had to be tested for safety, purity, and potency, and additional samples had to be sent for confirmation testing to the Food and Drug Administration (FDA).

Discouraged by such problems, in 1975, Lilly stopped producing experimental pneumococcal vaccines. Soon thereafter, in March 1976, Lilly also terminated most of its other vaccine research, development, and production programs. Lilly continues to produce only those vaccine products, such as rabies vaccine, which no other manufacturer makes.

In 1970, about 2 years after Lilly began work on pneumococcal vaccine under NIAID contract, Merck Sharp and Dohme intensified its own efforts to develop a pneumococcal vaccine. A leading vaccine innovator, developer, and producer, Merck had committed itself earlier to the task of developing and producing a meningococcal poly - saccharide vaccine for the U.S. Army. The company may have decided to invest in developing a pneumococcal polysaccharide vaccine because of the similarity of the research techniques and resources needed for this undertaking (Hilleman, 1978).

Working without direct Federal funding, Merck reportedly spent an estimated $6 million between 1970 and 1978 to develop a marketable pneumococcal polysaccharide vaccine. In the early 1970's, the company conducted independent clinical trials among gold miners in South Africa, demonstrating the safety and efficacy of its vaccine among tested populations (Smit, 1977). Levels of safety and efficacy for Merck's vaccine in these trials were comparable to those found for Lilly's product, which was used by Austrian in concurrent clinical trials among gold miners in South Africa (Austrian, et al., 1976).

Encouraged by these clinical trial results, Merck applied to FDA in 1976 for a license to manufacture and market its polyvalent pneumococcal capsular polysaccharide vac-

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'These diagnostic techniques are described in app. 3.5.

cine.[8] The company was issued a product license on November 21, 1977, and in February 1978, began marketing its 14-valent vaccine known as PNEUMOVAX.

A third company that recently pursued development of a pneumococcal polysaccharide vaccine is Lederle Laboratories. For the past 70 years, Lederle has been a relatively active vaccine reseacher and producer. It currently holds 19 product licenses and produces 10 vaccine products. Lederle is the sole producer of live poliovirus vaccine in the country.

According to an official company spokesman, Lederle began developing a pneumococcal vaccine in 1970 (Stessel, 1978), possibly in response to NIAID's initiative in spearheading basic research and development. Like Merck's, Lederle's work on pneumococcal vaccine was done without NIAID funding. Lederle's application for a pneumococcal vaccine product license was approved by FDA in August 1979. Lederle named its vaccine PNU-IMUNE.

THE ROLE OF FEDERAL FINANCING IN THE RESEARCH AND DEVELOPMENT OF PNEUMOCOCCAL VACCINE

The Federal Government's effort to stimulate vaccine research in academe, and to a lesser extent, in industry, centers on the dispersal, primarily through NIAID, of limited Federal funds for vaccine research and development. At present, no long-term, established criteria or specific objectives appear to direct either the size or the allocation of Federal vaccine research funds. Further, the expenditure of these funds can be influenced by factors other than quantitative assessment of public need.

The case study of pneumococcal vaccine illustrates the informal, often ad hoc process by which the public and the private sectors select diseases for intervention, develop methods of treatment or prevention, and evaluate the effectiveness of their efforts. NIAID's decision to fund pneumococcal vaccine research and development was not based on a comparative, quantitative assessment of pneumococcal diseases' threat to the public's health. All private and public sector efforts devoted to the development, evaluation, and marketing of pneumococcal vaccine were conducted in the absence of the following types of data: specific rates for the incidence, prevalence, morbidity, mortality, and medical costs of pneumococcal diseases. At no point during the development of this vaccine did HEW simultaneously solicit the collective advice and counsel from three of its agencies—BOB, NIAID, and CDC—for a systematic evaluation of the need for, or potential attributes of, a pneumococcal vaccine.

Two overriding factors led to the development and eventual marketing of pneumococcal vaccine. First, one man devoted his professional career to studying the mortality resulting from pneumococcal diseases and to developing a vaccine to prevent the occurrence of these diseases. Robert Austrian, virtually singlehandledly, convinced NIAID and at least one pharmaceutical company to spend jointly $12 million to research, develop, and test the pneumococcal polysaccharide vaccine now on the U.S. market. Second, in 1967, NIAID believed that the development of a pneumococcal polysaccharide vaccine to help prevent pneumococcal diseases was technologically feasible.

At the time NIAID committed itself to providing Federal funds for polyvalent pneumococcal polysaccharide vaccine research and development in 1967, no pharmaceutical

[8] Federal Government licensure of Merck's 14-valent pneumococcal polysaccharide vaccine is discussed in ch. 3.

company had committed itself to the development of a marketable product. NIAID's financial support greatly enhanced the coordination and visibility of pneumococcal vaccine research and development efforts.

Subsequent to NIAID's involvement, at least three pharmaceutical companies, Lilly, Merck, and Lederle, either started or intensified their pneumococcal research and development programs. That either Merck or Lederle would have pursued the independent development of a pneumococcal polysaccharide vaccine had NIAID not decided to become involved appears unlikely. Although neither company received direct Federal funding for basic research or product development, Merck did receive data generated from NIAID-funded research. When it subsequently applied for licensure to market its pneumococcal vaccine, Merck was required to submit to BOB some of its own data. Data that relate to specific manufacturing processes are considered to be trade secrets and are protected from public scrutiny by patent laws, but data such as those relating to the product's safety and efficacy are made public. Lederle, therefore, was able to use some of Merck's data in the development of its own product.

Merck and Lederle, the two companies that did not receive Federal funds for pneumococcal vaccine research and development, appear to remain strongly committed to their pneumococcal and other vaccine-related activities. Somewhat ironically, Eli Lilly, the one company that received Federal financing to develop pneumococca] polysaccharide vaccine, not only has since stopped all its work on pneumococca] vaccine, but has withdrawn from the vaccine market almost entirely. As reasons for- terminating the bulk of its vaccine research, development, and production activities, Lilly cited a number of economic factors, one of which was the cost of complying with certain Federal Government regulations.

The impact of various types of Federal Government policies on the commitment of the pharmaceutical industry to the research, development, and production of vaccines has not been thoroughly studied. For the pharmaceutical industry as a whole, the impact of particular Federal vaccine policies on private sector research, development, and production should be viewed in perspective with the impact of general economic factors, e.g., the size of the vaccine market and the profitability of vaccines compared to other pharmaceutical products.