

**AN OVERVIEW OF THE MARKET FOR VACCINES IN THE
UNITED STATES**

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I. INTRODUCTION

The purpose of this paper is to describe the supply side of vaccine markets, attempt to explain factors that generate this structure such as economies of scale, regulatory and pricing policies, and financial conditions, and how these factors impact the existence of shortages and supply interruptions in these markets. The paper should be thought of as a traditional industrial organization approach to these markets. One critical and important caveat must be made up front. The normal process of the industrial organization approach would be initially to describe the structure of the markets as we do and for which we have reasonable data sources. The next step would be to construct hypotheses generated from economic theories and then conduct empirical estimation and analysis to test the validity of these hypotheses. While we can construct hypotheses, we do not have data to conduct formal econometric analysis. Therefore, much of our analysis beyond the descriptive aspects of the markets is based on antidotal evidence and speculation. On some issues this evidence is very strong and we are quite confident. On others we must resort to speculation in which case our use of qualifiers must be taken seriously.

Worldwide production of vaccines is a relatively small market when compared to pharmaceuticals. Vaccines (sometimes referred to as *biologics*) represent approximately US\$6 billion per year. This is only two percent of the worldwide pharmaceutical market. This may be an important factor in explaining why many producers of vaccines have exited from these markets only to enter the much larger pharmaceutical markets. Of course,

while the market size may not be overwhelming, the successful history of vaccines includes eradication of diseases that have claimed millions of human lives. Benefit cost ratios for vaccines typically are very large. Many diseases have been totally eradicated in high-income countries and other indications occur only sporadically in those countries.

The last quarter of the 20th century witnessed both great successes for vaccines as well as crises. Many new childhood and adult vaccines were discovered, tested and are now on the market. R&D expenditures took a dip from the 1970s to the mid 1980s but recovered in the last few years of that decade and presently appear to be increasing.

(Grabowski and Vernon (1997), p 10. and Mercer (2002)¹) The overwhelming burden of tort liability cases resulted in bold policy actions in the U.S. with the establishment of the Vaccine Injury Compensation Program in 1988. The program has reduced but not eliminated tort liability exposure.

Vaccine markets have been characterized by increased incidents of shortages over the past few years that spread across many product lines and emanate from a variety of causes. These shortages are worldwide and affect vaccines against indications including DTP (diphtheria-tetanus-pertussis), MMR (measles, meningitis, and rubella), OPV (polio), TT (tetanus toxoid), BCG (tuberculosis), and yellow fever. The supply interruptions have resulted in unmet demand in these established product lines, generating serious concerns about health and safety. This has obvious implications about the future production, regulatory, purchasing and generation of new vaccines directed at other indications.

¹ Throughout this paper we refer extensively to two reports prepared by Mercer Management Consulting. Throughout the text we will refer to the 1995 report as Mercer (1995) and the 2002 report as Mercer (2002). There are no page numbers on Mercer (2002).

The total number of producers of vaccines, across all product lines, has never been large and is declining. Further very few vaccines directed at a particular indication are substitutable. Therefore, markets of vaccines for specific indications have a very small number of producers. At least three of the basic childhood vaccines are provided by single producers. The implications of this continued drop in producers should be clear: at any point in time, a particular market serviced by a single supplier is open to random shortages caused by any episode which causes the producer to temporarily (or longer) cease production. In markets served by a small number of producers, producers generally are not able to quickly increase production to overcome shortages caused by an unexpected interruption in production by another firm. Likewise, stockpiles held by CDC are not always adequate to alleviate these problems. In a 1985 publication, DeBrock and Grabowski concluded "...the sole-supplier situation poses a threat to the continued supply of some vaccines."² Eight years later in another publication, Arnould and DeBrock wrote "Significant concern about supply interruptions results from the existence of single producers of many vaccines, including 10 of the 15 recommended childhood vaccines."³ The number of producers continues to decline as the number of vaccines provided by a single supplier increases.

The events in 2001 are compelling proof that the warnings of earlier analyses were more than just speculation. In 2000 and 2001, many vaccine markets fell victim to supply disruption and shortages. Vaccines that are in continuous demand, such as tetanus and influenza, experienced some of the sharper problems. In March of 2000, there were two

² DeBrock and Grabowski (1985), page 61.

³ Arnould and DeBrock (1993), page 102.

major producers of tetanus vaccine in the United States, Aventis Pasteur and Wyeth-Ayerst, and no shortages. By early January, Wyeth had ceased production of the vaccine, leaving Aventis as the only supplier.⁴ Aventis could not scale up production rapidly enough to meet demand and was forced to ration supply. The story of shortages could be retold in the markets for MMR, Varicella, and Pneumococcal Conjugate vaccines. Each case had different circumstances (these are described in detail in other papers), but the resulting shortage was similar.

As of July 2002, the CDC's National Immunization Program indicated that in most cases, the specific shortages were no longer as large of a problem in the U.S. Table I lists the NIP shortage information (www.cdc.gov/nip).

This is much improved over the situation just a few months earlier. In May of 2002, the CDC considered there to be shortages in DTaP, Td, MMR, Varicella, and PCV vaccines. Hib was classified similarly to the July table, with four to six week delays rather than the two to four week delays of July.

The causes of these shortages help to explain why the relief could come so quickly. Some were production problems, some were due to incorrect levels of stockpiles, and some were due to plant renovation. But, in each case the consistent theme was the fact that there are so few producers in the market. Interruptions in supply by one producer do occur and the supply reduction cannot readily be made up by other suppliers, even in vaccine markets in which multiple suppliers exists.. The result is that supply consistency will continue to be brittle and shortages likely.

⁴ Brichacek (2001) indicates that the Wyeth pullout was precipitated by a June 2000 problem with the FDA concerning substandard acellular pertussis vaccine.

Table I
National Vaccine Supply Shortages⁵

National Vaccine Supply Shortages			
Vaccine	Shortage	Expected Duration	Temporary Change from Routine Recommendation
Hepatitis B ⁶	No		
Diphtheria, Tetanus, & Pertussis (DTaP)	No ⁷		
Td	No		
Haemophilus influenzae type B (Hib) ⁸	See note ⁹		
Inactivated Polio (IPV)	No		
Measles, Mumps, & Rubella (MMR)	No ¹⁰		
Varicella	No		
Pneumococcal (PCV)	Yes	last quarter of 2002 or later	Yes http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5050a4.htm
Hepatitis A	No		

This paper will construct an economic description of the supply side of the vaccine industry. The focus will be on producers, production, and provision. Even though pricing and financial outcomes are the main focus of papers being prepared by other researchers,

⁵ Source: <http://www.cdc.gov/nip>. Only those vaccines included on the recommended childhood immunization schedule are included in this update.

⁶ Two to four weeks are required to fill Hepatitis B/Hib combination (COMVAX) orders. Full availability should return by fall 2002.

⁷ Vaccine supplies are sufficient to return to the routine schedule as recommended by the ACIP/AAP. However, additional vaccine is not available for ambitious recall or special initiative programs at this time.

⁸ See note 3.

⁹ Hib vaccine is available from Aventis Pasteur. Hib vaccine orders from Wyeth require up to 60 days to fill and their supply is not likely to improve in 2002. Orders from Merck are taking 6 to 8 weeks to fill with little improvement expected before December 2002.

¹⁰ See Note 4.

some explanation is necessary to explain how the dynamics of such considerations impact the structure of the markets and ultimately the existence of shortages.

The next section will discuss the history of producers and production in the U.S. While our focus is the U.S. market, vaccines production and demand are global in nature. As such, the international market must be considered. The international production of vaccines does not play a key role in the current provision of vaccines in the U.S. However, the continued existence of these international vaccine producers implies a potential new source of vaccines for the U.S. market. The remaining sections describe demand conditions, delivery systems, R&D, and then conclude with section that attempts to explain factors responsible for the structure of vaccine markets.

II. THE VACCINE MARKET

The phrase “vaccine industry” implies a certain market with firms producing a product or products that are substitutes and therefore competitive. In fact, this is a misnomer. There are numerous producers of *vaccines* but the vaccines they produce are, in the traditional sense used by economists, in many different markets. The product market for the “vaccine industry” is really a collection of a number of different markets, each representing a different product (vaccine) aimed at a different indication. For example, the MMR vaccine certainly is not in competition with the Polio vaccine.

Worldwidesales of vaccines is currently about US\$4.5 billion.¹¹ The majority of production is concentrated in a few firms. The 2000 sales figures for themajor producing firms are as follows:

Manufacturer	2000 Vaccine Sales
GlaxoSmithKline	\$1,250m
AventisPasteur	\$1,005m
Wyeth	\$980m
Merck&Co	\$952m

Vaccine Production

In the middle of the twentieth century, diphtheria, tetanus, pertussis and smallpox were the only available childhood vaccines. In 1985 the number of vaccines recommended for children had grown to only 5. Currently, the American Academy of Pediatrics recommends that children receive vaccinations against 13 indications by the age of two.¹² In addition to these childhood vaccines, the array of adult vaccines has also grown.

Table II lists all domestically produced vaccines currently licensed for use in the United States, with the manufacture and the date the vaccine was given approval for sale and use.

¹¹ This is a large figure as vaccines go, but still amounts to only 2 percent of the global pharmaceutical market.

¹² These include Hepatitis B, Diptheria, Tetanus, Pertussis, Haemophilus Influenza Type b, Polio, Measles, Mumps, Rubella, Varicella, Pneumococcal, Hepatitis A, and influenza (yearly). While some of these are combined in one injection, some indications require multiple injections over time. The net result has been that since 1985, the number injections a child must receive by the age of two has more than tripled.

Table II
U.S. Domestic Vaccine Producers and Products

Company	Generic name	US approval date
BIOPORT CORPORATION (MICHIGAN DEPARTMENT OF PUBLIC HEALTH)	anthrax vaccine adsorbed	1970
ALLERGAN	botulinum toxin type A	1991
WYETH (WYETH LABORATORIES, INC.)	cholera vaccine	1952
BIOPORT CORPORATION	diphtheria & tetanus toxoids & pertussis vaccine adsorbed	1998
BIOPORT CORPORATION	diphtheria & tetanus toxoids adsorbed	1970
BIOPORT CORPORATION	diphtheria toxoid adsorbed	1998
WYETH (LEDERLE-PRAXIS)	haemophilus b conjugate vaccine	1988
MERCK & CO (MERCK, SHARPE AND DOHME)	haemophilus b conjugate vaccine	1989
MERCK & CO	haemophilus b conjugate vaccine & hepatitis B (recombinant) vaccine	1996
WYETH (PRAXIS BIOLOGICS)	haemophilus B vaccine	1990
WYETH (AMERICAN CYANAMID)	haemophilus vaccine	1985
MERCK & CO	hepatitis B vaccine	1982
MERCK & CO	hepatitis-A vaccine, inactivated	1996
BIOGEN	hepatitis-B vaccine	1989
WYETH (WYETH LABORATORIES)	influenza virus vaccine	1945
WYETH (WYETH LABORATORIES)	influenza virus vaccine	1961
KING PHARMACEUTICALS (PARKEDALE PHARMACEUTICALS)	influenza virus vaccine	1998
MERCK & CO	measles and mumps virus vaccine live	1973
MERCK & CO	measles and rubella virus vaccine live	1971
MERCK & CO	measles virus vaccine live	1963
MERCK & CO	measles, mumps, and rubella virus vaccine live	1971
MERCK & CO	mumps virus vaccine live	1967
BIOPORT CORPORATION	pertussis vaccine adsorbed	1998
GREER LABORATORIES	plague vaccine	1994
WYETH (WYETH AYERST)	pneumococcal 7-valent conjugate vaccine	2000
MERCK & CO (MERCK, SHARPE AND DOHME)	pneumococcal vaccine polyvalent	1977
WYETH (LEDERLE LABORATORIES)	pneumococcal vaccine polyvalent	1979
WYETH (WYETH-LEDERLE)	poliovirus vaccine live oral trivalent	1963
WYETH (WYETH-LEDERLE)	poliovirus vaccine live oral type I	1962
WYETH (WYETH-LEDERLE)	poliovirus vaccine live oral type II	1962
WYETH (WYETH-LEDERLE)	poliovirus vaccine live oral type III	1962
HOLLISTER-STIER LABORATORIES	polyvalent bacterial vaccines	1999
WYETH (WYETH-AYERST)	rabies vaccine	1982
CHIRON (BEHRINGWERKE)	rabies vaccine	1997
BIOPORT CORPORATION	rabies vaccine adsorbed	1998
MERCK & CO	rubella and mumps virus vaccine live	1970
MERCK & CO	rubella virus vaccine live	1969
BIOPORT CORPORATION	tetanus toxoid adsorbed	1998
WYETH (WYETH-LEDERLE)	typhoid vaccine	1952
MERCK & CO	varicella virus vaccine live	1995
BIOPORT CORPORATION (MICHIGAN DEPARTMENT OF PUBLIC HEALTH)	anthrax vaccine adsorbed	1970
ALLERGAN	botulinum toxin type A	1991
WYETH (WYETH LABORATORIES, INC.)	cholera vaccine	1952

Source: Tufts Center for the Study of Drug Development, Tufts University, 2002

As can be seen from the table, some manufacturers are more active than others. Wyeth has 16 licenses and Merck has 13. However, there are 7 manufacturers with just one license in the U.S.

In addition to these domestically supplied vaccines, foreign producers have also received approval for sales of vaccines in the U.S. Table III lists all foreign-produced vaccines, again by manufacturer and year of approval.

Table III
Foreign Suppliers of Vaccine to U.S. Market

Company	Country	Generic name	US approval date
STATENS SERUM INSTITUT	DENMARK	diphtheria toxoid	1998
STATENS SERUM INSTITUT	DENMARK	tetanus & diphtheria toxoids	1998
STATENS SERUM INSTITUT	DENMARK	tetanus toxoid	1998
AVENTIS (PASTEUR MERIEUX CONNAUGHT)	FRANCE	acellular pertussis DTP	1992
AVENTIS (AVENTIS PASTEUR)	FRANCE	BCG Live vaccine	1990
AVENTIS (AVENTIS PASTEUR)	FRANCE	BCG vaccine	1998
AVENTIS (AVENTIS PASTEUR)	FRANCE	conjugated haemophilus influenzae b and diphtheria, tetanus, and acellular pertussis vaccine	1993
AVENTIS (AVENTIS PASTEUR)	FRANCE	CPDT vaccine	2002
AVENTIS (AVENTIS PASTEUR)	FRANCE	diphtheria & tetanus toxoids & pertussis vaccine adsorbed	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	diphtheria & tetanus toxoids adsorbed	1984
AVENTIS (AVENTIS PASTEUR)	FRANCE	diphtheria & tetanus toxoids adsorbed	1997
AVENTIS (AVENTIS PASTEUR)	FRANCE	diphtheria & tetanus toxoids adsorbed, for adult use	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	haemophilus B conjugate vaccine	1987
AVENTIS (AVENTIS PASTEUR)	FRANCE	haemophilus b conjugate vaccine (tetanus toxoid conjugate)	1993
AVENTIS (AVENTIS PASTEUR)	FRANCE	haemophilus b conjugate vaccine/diphtheria, tetanus toxoids, acellular pertussis vaccine in combination	1996
AVENTIS (AVENTIS PASTEUR)	FRANCE	influenza virus vaccine	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	meningococcal polysaccharide vaccine, group A	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	meningococcal polysaccharide vaccine, group C	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	meningococcal polysaccharide vaccine, groups A, C, Y and W-135 combined	1981
AVENTIS (AVENTIS PASTEUR)	FRANCE	pertussis vaccine	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	poliovirus vaccine inactivated	1987
AVENTIS (AVENTIS PASTEUR)	FRANCE	poliovirus vaccine inactivated	1990
AVENTIS (AVENTIS PASTEUR)	FRANCE	rabies vaccine	1980
AVENTIS (AVENTIS PASTEUR)	FRANCE	rabies vaccine	1991
AVENTIS (AVENTIS PASTEUR)	FRANCE	smallpox vaccine	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	tetanus toxoid	1943
AVENTIS (AVENTIS PASTEUR)	FRANCE	tetanus toxoid	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	tetanus toxoid adsorbed	1978
AVENTIS (AVENTIS PASTEUR)	FRANCE	yellow fever vaccine	1978
TAKEDA CHEMICAL INDUSTRIES, LTD.	JAPAN	acellular pertussis vaccine concentrate	1991
RESEARCH FOUNDATION FOR MICROBIAL DISEASES	JAPAN	japanese encephalitis virus vaccine inactivated	1992
AKZO NOBEL (ORGANON TEKNIKA CORP.)	NETHERLANDS	BCG vaccine	1989
CHEIL JEDANG	SOUTH KOREA	hepatitis-B vaccine	1988
BERNA SA (SWISS SERUM AND VACCINE INSTITUTE)	SWITZERLAND	tetanus toxoid adsorbed	1970
BERNA SA (SWISS SERUM AND VACCINE INSTITUTE)	SWITZERLAND	typhoid vaccine live oral	1989
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UK	diphtheria & tetanus toxoids & acellular pertussis vaccine adsorbed	1997
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UK	hepatitis A Inactivated & Hepatitis B (recombinant) vaccine	2001
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UK	hepatitis B vaccine (recombinant)	1989
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UK	hepatitis-A vaccine, inactivated	1995
POWDERJECT PHARMACEUTICALS (MEDEVA PHARMA)	UK	influenza virus vaccine	1998
SHIRE (BIOCHEM PHARMA)	UK		2000
STATENS SERUM INSTITUT	DENMARK	diphtheria toxoid	1998
STATENS SERUM INSTITUT	DENMARK	tetanus & diphtheria toxoids	1998
STATENS SERUM INSTITUT	DENMARK	tetanus toxoid	1998
AVENTIS (PASTEUR MERIEUX CONNAUGHT)	FRANCE	acellular pertussis DTP	1992

Source: Tufts Center for the Study of Drug Development, Tufts University, 2002

Single Seller Markets

Of all the vaccines approved, many are currently in the position of having only a single seller in the market. Tables II and III established that there are many vaccines approved and on the market. However, the danger of supply interruptions remains very real, particularly in markets reduced to single or even dual-supplier status.

Table IV groups the vaccines by number of active licenses(in the US). The single producer grouping is the most prevalent. However, several of the vaccines within that category appear to be very close substitutes for each other, but this is not the case where one producer holds all licenses to blended vaccines such as MMR.

**Table IV
U.S. Vaccines by Number of Licensed Producers**

Number of Licensed Manufacturers	Vaccine
1	anthrax vaccine adsorbed botulinum toxin type A cholera vaccine diphtheria toxoid haemophilus B vaccine haemophilus vaccine hepatitis A Inactivated & Hepatitis B (recombinant) vaccine measles virus vaccine live measles and mumps virus vaccine live measles, mumps, and rubella virus vaccine live measles and rubella virus vaccine live pertussis vaccine plague vaccine smallpox vaccine typhoid vaccine varicella virus vaccine live
2	diphtheria & tetanus toxoids & pertussis vaccine adsorbed haemophilus B conjugate vaccine haemophilus b conjugate vaccine/diphtheria, tetanus toxoids, acellular pertussis vaccine in combination hepatitis B vaccine mumps virus vaccine live poliovirus vaccine inactivated

	rabies vaccine tetanus & diphtheria toxoids yellow fever vaccine
3	influenza virus vaccine japanese encephalitis virus vaccine inactivated meningococcal polysaccharide vaccine, group A pneumococcal 7-valent conjugate vaccine rubella and mumps virus vaccine live
4	BCG Live vaccine acellular pertussis DTP
5	hepatitis-A vaccine, inactivated tetanus toxoid
8	diphtheria & tetanus toxoids adsorbed poliovirus vaccine live oral trivalent

These situations are somewhat clarified in Table V which cross tabulates the vaccines by the producers holding the U.S. license. Table V provides such a view of the data.

Table V
Vaccine Licenses by Manufacturer

Generic name	KAZO NOBEL (ORGANON TEKNIKA CORP.)	ALLERGAN	AVENTIS	BERNARD SA (SWISS SERUM AND VACCINE INSTITUTE)	BIOGEN	BIPORT CORPORATION	CHEIL JEDANG	CHIRON	GLAXOSMITHKLINE	GREER	HOLLISTER-STIER LABS	KING PHARMACEUTICALS	MERCK	POMERLEAU	RESEARCH INSTITUTION FÜR BIOTRUBDAL DISEASES	SHIRE	STATENS SERUM INSTITUT	TAKENDA	WYETH	Grand Total
acellular pertussis DTP			1																	1
acellular pertussis vaccine concentrate																			1	1
anthrax vaccine adsorbed						1														1
BCG Live vaccine			1																	1
BCG vaccine	1		1																	2
botulinum toxin type A		1																		1
cholera vaccine																				1
conjugated haemophilus influenzae b and diphtheria, tetanus, and acellular pertussis vaccine			1																	1
CPDT vaccine			1																	1
diphtheria & tetanus toxoids & pertussis vaccine adsorbed			1			1														2
diphtheria & tetanus toxoids adsorbed			2			1														3
diphtheria & tetanus toxoids adsorbed, for adult use			1																	1
diphtheria & tetanus toxoids & acellular pertussis vaccine adsorbed									1											1
diphtheria toxoid																		1		1
diphtheria toxoid adsorbed						1														1
haemophilus B conjugate vaccine			1																	1
haemophilus b conjugate vaccine & hepatitis B (recombinant) vaccine													1							1
haemophilus b conjugate vaccine (tetanus toxoid conjugate)			1																	1
haemophilus b conjugate vaccine/diphtheria, tetanus toxoids, acellular pertussis vaccine in combination			1																	1
haemophilus B vaccine																				1
haemophilus vaccine																				1
hepatitis A inactivated & Hepatitis B (recombinant) vaccine									2											2
hepatitis B vaccine													1							1
hepatitis B vaccine (recombinant)									2											2
hepatitis-A vaccine, inactivated									1				1							2
hepatitis-B vaccine																				1
influenza virus vaccine			1		1		1					1		1						5
japanese encephalitis virus vaccine inactivated															1					1
measles and mumps virus vaccine live													1							1
measles and rubella virus vaccine live													1							1
measles virus vaccine live													1							1
measles, mumps, and rubella virus vaccine live													1							1
meningococcal polysaccharide vaccine, group A			1																	1
meningococcal polysaccharide vaccine, group C			1																	1
meningococcal polysaccharide vaccine, groups A, C, Y and W-135 combined			1																	1
mumps virus vaccine live													1							1
pertussis vaccine			1																	1
pertussis vaccine adsorbed						1														1
plague vaccine										1										1
pneumococcal 7-valent conjugate vaccine																				1
pneumococcal vaccine, polyvalent													1							1
poliovirus vaccine inactivated			2																	2
poliovirus vaccine live oral trivalent																				1
poliovirus vaccine live oral type I																				1
poliovirus vaccine live oral type II																				1
poliovirus vaccine live oral type III																				1
polyvalent bacterial vaccines											1									1
rabies vaccine			2					1												3
rabies vaccine adsorbed							1													1
rubella and mumps virus vaccine live													1							1
rubella virus vaccine live													1							1
smallpox vaccine			1																	1
tetanus & diphtheria toxoids																				1
tetanus toxoid			2															1		3
tetanus toxoid adsorbed			1	1		1														3
typhoid vaccine																				1

The far right column indicates that a number of the vaccines are produced in single-seller markets. However, some of the vaccines can work as substitutes for others, such as polio inactivated versus polio live.

Exit

Over the past few decades, both domestic and international manufacturers of vaccines, have withdrawn from the U.S. market. Of the 146 vaccines approved since 1933, 62 have subsequently withdrawn from the market. Some of these withdrawals represent situations where the particular approved vaccine was replaced by a more effective or safer alternative. As an example, consider the replacement of DTP

Table VI
Approved Vaccines Withdrawn From U.S. Market

Company	Country Name	Generic name
MERCK & CO (MERCK, SHARPE AND DOHME)	UNITED STATES	tetanus toxoid
WYETH (LEDERLE)	UNITED STATES	staphylococcus toxoid
ELI LILLY	UNITED STATES	tetanus toxoids
BAYER CORP. (CUTTER)	GERMANY	tetanus toxoid
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	tetanus toxoid
MERCK & CO (MERCK, SHARPE AND DOHME)	UNITED STATES	typhus vaccine
WYETH (LEDERLE)	UNITED STATES	cholera vaccine
BAYER CORP. (CUTTER)	GERMANY	plague vaccine
WYETH (LEDERLE)	UNITED STATES	Rocky mountain spotted fever vaccine
WYETH (WYETH LABORATORIES)	UNITED STATES	smallpox vaccine (vaccinia)
WYETH (WYETH-LEDERLE)	UNITED STATES	tetanus toxoid
MERCK & CO (MERCK, SHARPE AND DOHME)	UNITED STATES	influenza virus vaccine
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	influenza virus vaccine
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	diphtheria and tetanus toxoids and pertussis vaccine adsorbed
BRISTOL-MYERS SQUIBB (E.R. SQUIBB)	UNITED STATES	6-valent pneumococcal vaccine
ELI LILLY	UNITED STATES	diphtheria and tetanus toxoids
MERCK & CO	UNITED STATES	diphtheria and tetanus toxoids and pertussis vaccine adsorbed
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	diphtheria and tetanus toxoids
WYETH (LEDERLE)	UNITED STATES	gas gangrene polyvalent antitoxin
MERCK & CO (MERCK, SHARPE AND DOHME)	UNITED STATES	cholera vaccine
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	diphtheria and tetanus toxoids and pertussis vaccine
WYETH	UNITED STATES	diphtheria toxoid adsorbed
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	poliomyelitis vaccine
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	adenovirus vaccine
DELMONT LABORATORIES	UNITED STATES	polyvalent bacterial antigens
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	adenovirus and influenza vaccines combined aluminum phosphate adsorbed
PFIZER	UNITED STATES	Polio vaccine, live, oral Type1
PFIZER	UNITED STATES	Polio vaccine, live, oral Type2
PFIZER	UNITED STATES	Polio vaccine, live, oral Type3
GLAXOSMITHKLINE (GLAXO WELLCOME)	UNITED KINGDOM	BCG vaccine
MERCK & CO (MERCK, SHARPE AND DOHME)	UNITED STATES	typhoid vaccine
PFIZER (PARKE, DAVIS AND CO)	UNITED STATES	diphtheria, tetanus toxoids, pertussis vaccine adsorbed, poliomyelitis vaccine
MERCK & CO (MERCK, SHARPE AND DOHME)	UNITED STATES	smallpox vaccine
WYETH (LEDERLE)	UNITED STATES	measles vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	smallpox vaccine
MERCK & CO (MERCK, SHARPE AND DOHME)	UNITED STATES	measles-smallpox vaccine, live
WYETH (LEDERLE)	UNITED STATES	typhus vaccine
WYETH (LEDERLE LABORATORIES)	UNITED STATES	diphtheria & tetanus toxoids & pertussis vaccine adsorbed
WYETH (WYETH LABORATORIES)	UNITED STATES	diphtheria & tetanus toxoids adsorbed

WYETH (WYETH LABORATORIES)	UNITED STATES	diphtheria & tetanus toxoids adsorbed for adult use
WYETH (WYETH LABORATORIES)	UNITED STATES	diphtheria & tetanus toxoids adsorbed
WYETH (WYETH LABORATORIES)	UNITED STATES	diphtheria & tetanus toxoids adsorbed for adult use
WYETH (WYETH LABORATORIES, INC.)	UNITED STATES	diphtheria & tetanus toxoids & pertussis vaccine adsorbed
WYETH (WYETH-LEDERLE)	UNITED STATES	tetanus toxoid adsorbed

Source: Tufts Center for the Study of Drug Development, Tufts University, 2002

(diphtheria, tetanus and pertussis) by the safer DTaP. Another reason for withdrawal that would not be considered troublesome is the introduction of combination vaccines, replacing “single-indication” vaccine in vaccination schedules. Much current R&D and product testing is going into expansion of combination vaccines because they generally reduce the number of doses, and even though vaccine combination may be more expensive labor and other costs associated with the inoculation are reduced.

Alternatively, some exit is alleged to be caused by economic factors that result in unprofitable operation, or low returns relative to those from the production of pharmaceuticals. These exits are almost certain to reflect rational behavior on the part of the manufacturer. These could include situations where demand is not strong enough to warrant continued production.¹³ Another reason for exit could be that costs of operation and compliance may be too great to support more than one producer. Often the result could be a single or dual supplier or no-supplier of the entire specific vaccine segment, as is the case with the vaccine for indicators of Lyme disease. While the latter is clearly worse, neither situation is attractive. These issues will be addressed in more detail in section VI of this chapter.

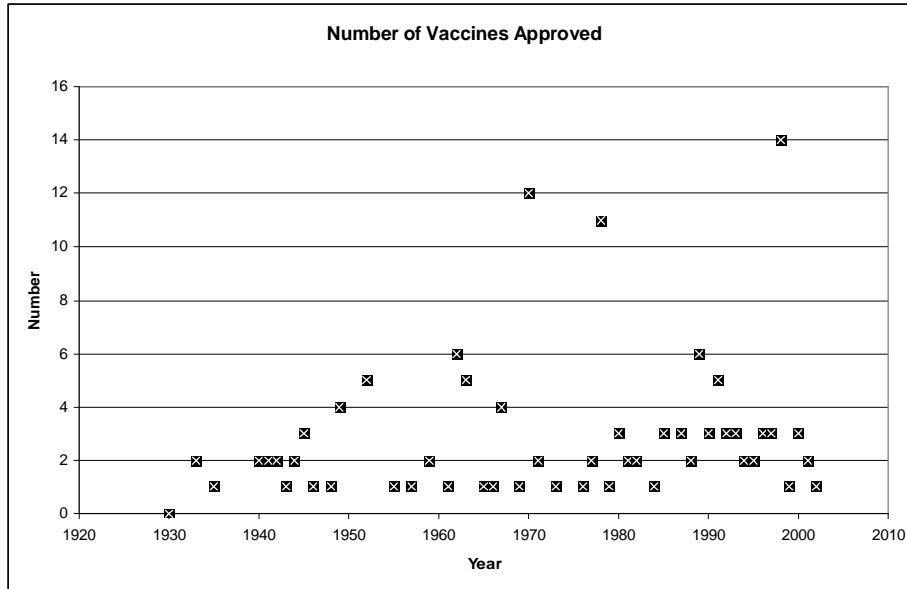
¹³ FOOTNOTE ABOUT GLAXO pullout of Lyme disease market due to lack of demand.

Potential Entrants

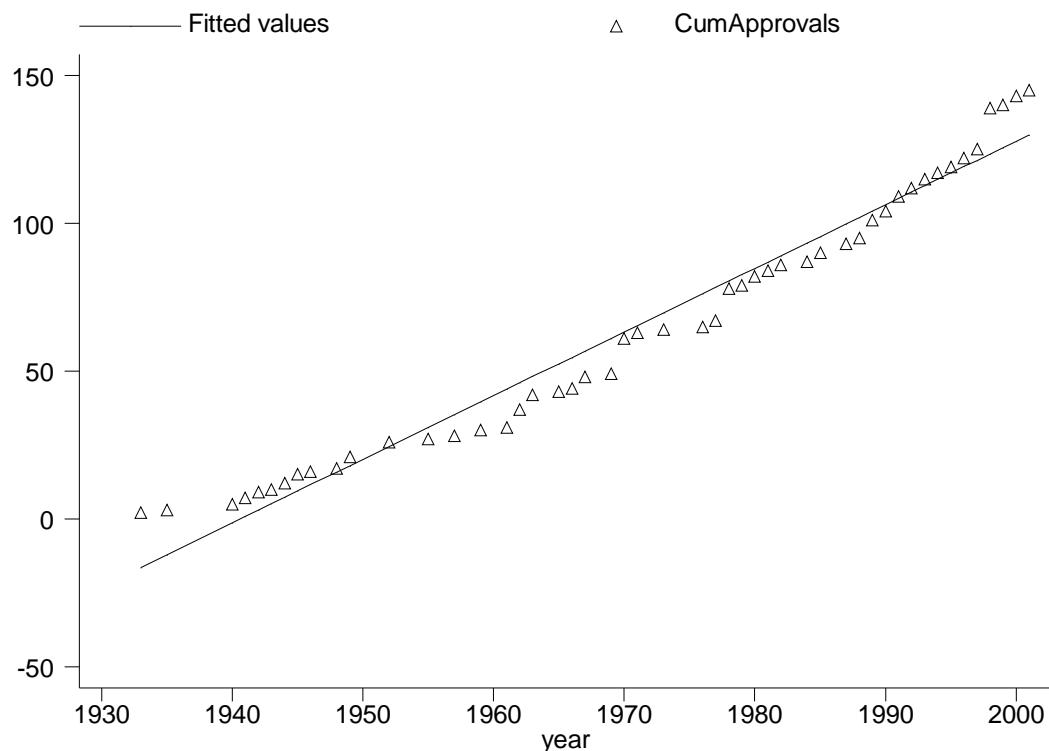
The data above indicate that there are several vaccine markets with single-producer status. These products present the most serious danger of supply disruption. However, to the extent that there are new competitors available to “step in” in the event of such an interruption, the problem is not nearly so severe. Therefore, we must consider the potential for new entry. New entry would have to come by way of presenting a vaccine that could achieve approval for sale and distribution in the United States. The pace of new approval has continued to pick up. The decade of the nineties witnessed 39 new approvals, the most in a decade in history. Nearly half of all vaccine approvals have occurred since 1980. The following figure describes U.S. vaccine approval activity from 1933 to 2001. A simple analysis of the trend of cumulative approvals over time reveals a forecast that just over two licenses per year are issued in the United States.¹⁴

¹⁴ Of course, these are gross cumulative licenses. We have no data on withdrawal dates of vaccines that exit the market. However, it is clear that the net change in a year will be less than the forecast time trend coefficient.

Figure 1
U.S. Vaccine Approval



Source	SS	df	MS	Number of obs =	50
			F(1, 48)	=	1378.92
Model	95210.5562	1	95210.5562	Prob > F	= 0.0000
Residual	3314.26381	48	69.0471628	R-squared	= 0.9664
			Adj R-squared	=	0.9657
Total	98524.82	49	2010.71061	Root MSE	= 8.3095
CumApprovals	Coef.	Std. Err.	t	P>t	[95% Conf. Interval]
year	2.152887	.0579764	37.13	0.000	2.036317 2.269456
_cons	-4178.002	114.324	-36.55	0.000	-4407.866 -3948.138



These licenses come from products that are developed both domestically and in other countries. Human vaccines that are currently approved for distribution outside of the United States seem to be the most attractive candidates for entering the approval process. Such products have completed the R&D cycle and are being used to immunize populations in these other countries. Table VII presents a list of such “foreign launched” vaccines. The table indicates the producer and the country that has approved the vaccine for distribution.

Many of these vaccines appear to fit nicely with the markets that produce the most concern, the single producer markets shown in Table V above. Of course, they cannot be sold in the U.S. without completing the licensing procedure. And, to the extent this licensing process is arduous, competition from these vaccines may be delayed or non-existent. However, in the event of a disastrous supply interruption in one of the domestic

single-seller markets, a vaccine that has proven to be safe and effective in, for example, Europe should be considered as at least a temporary solution.

**Table VII
Active Foreign Vaccines Not Yet Approved in the U.S.**

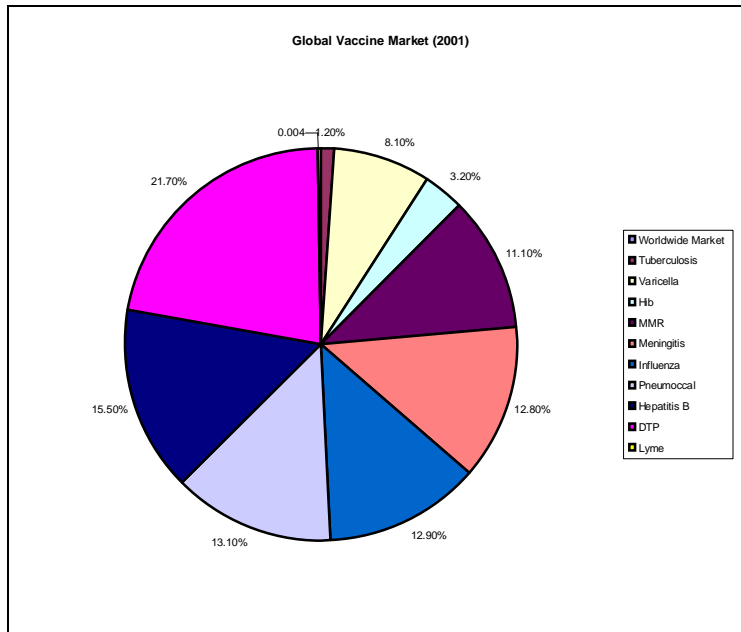
Company	Country	Generic name
AVENTIS (PASTEUR MERIEUX MSD)	FRANCE	streptococcus pneumoniae vaccine
WOCKHARDT	INDIA	hepatitis-B vaccine
SHIRE	UNITED KINGDOM	BCG live
AVENTIS (AVENTIS PASTEUR)	FRANCE	pentavalent DTP vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	DTP-polio vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	diphtheria, polio, and tetanus vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	diphtheria and tetanus vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	hepatitis A and typhoid vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	influenza vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	rabies vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	varicella vaccine
AVENTIS (PASTEUR MERIEUX)	FRANCE	hepatitis-B vaccine
BERNA SA	SWITZERLAND	influenza vaccine, injected
BERNA SA	SWITZERLAND	influenza vaccine
CADILA	INDIA	leprosy vaccine
CHIRON	UNITED STATES	cholera vaccine
CHIRON	UNITED STATES	diphtheria vaccine
CHIRON	UNITED STATES	diphtheria, tetanus, and polio vaccine
CHIRON	UNITED STATES	diphtheria and tetanus vaccine
CHIRON	UNITED STATES	measles vaccine
CHIRON	UNITED STATES	measles and mumps vaccine
CHIRON	UNITED STATES	measles, mumps, rubella vaccine
CHIRON	UNITED STATES	measles and rubella vaccine
CHIRON	UNITED STATES	mumps vaccine
CHIRON	UNITED STATES	rubella vaccine
CHIRON	UNITED STATES	tuberculosis vaccine
CHIRON	UNITED STATES	typhoid fever vaccine
CHIRON (BIOCINE)	UNITED STATES	haemophilus vaccine
CHIRON (BIOCINE)	UNITED STATES	acellular pertussis with diphtheria and tetanus (recombinant)
CHIRON (BIOCINE)	UNITED STATES	inactivated polio
CHIRON (CHIRON BEHRING GMBH)	UNITED STATES	influenza vaccine
COMMONWEALTH SERUM LABORATORIES	AUSTRALIA	ADT vaccine
COMMONWEALTH SERUM LABORATORIES	AUSTRALIA	influenza vaccine
COMMONWEALTH SERUM LABORATORIES	AUSTRALIA	Q-fever vaccine
COMMONWEALTH SERUM LABORATORIES	AUSTRALIA	rubella vaccine
GLAXOSMITHKLINE (SB BIOMED)	UNITED KINGDOM	diphtheria, tetanus, whole cell pertussis, rDNA hepatitis vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	DTaP + Hib
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	infection, influenza
ICN	UNITED STATES	lactobacillus vaccine
ICN	UNITED STATES	urinary tract infection vaccine
KAKETSUKEN	JAPAN	hepatitis-B vaccine
KAKETSUKEN	JAPAN	hepatitis-A vaccine
KOREA GREEN CROSS	SOUTH KOREA	typhoid vaccine
LG CHEMICAL	SOUTH KOREA	hepatitis-B vaccine
LG CHEMICAL	SOUTH KOREA	varicella vaccine
DAIICHI-KANGARU	JAPAN	hepatitis-B vaccine
NOVARTIS	SWITZERLAND	influenza vaccine
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	polio vaccine, injectable
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	tetanus
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	tuberculosis vaccine
POWDERJECT PHARMACEUTICALS (SBL VACCIN)	UNITED KINGDOM	cholera vaccine
RESEARCH DEVELOPMENT CORP.	JAPAN	hepatitis B vaccine
RHEIN BIOTECH	NETHERLANDS	hepatitis B vaccine
ROCHE (GENENTECH)	UNITED STATES	hepatitis-B vaccine
SHANTHA	INDIA	hepatitis-B vaccine

SHIRE (BIOCHEM VACCINES)	UNITED KINGDOM	split virus influenza vaccine
SOLVAY	BELGIUM	influenza vaccine
BAVARIAN NORDIC RESEARCH INSTITUTE	DENMARK	smallpox vaccine

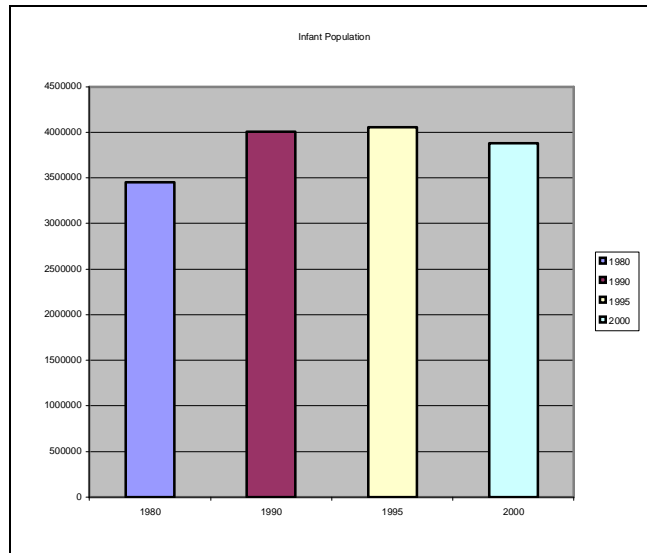
Critical Issues: Even though there has been a very substantial decline in the number of companies that produce, the total number remains large on a global basis. However, when the vaccine industry is divided into real product and geographic markets the number is very small. A number of vaccine markets in the US currently are served by one producer. In single producer markets there is no one available to accommodate supply interruptions. In two or three firm markets, when a supply interruption is generated by one firm, it is very difficult for the remaining firms to scale up on short notice to accommodate the supply shortage. Thus, shortages generated by supply interruptions and firms exiting from markets are very closely linked to market structure.

III. CURRENT VACCINE DEMAND

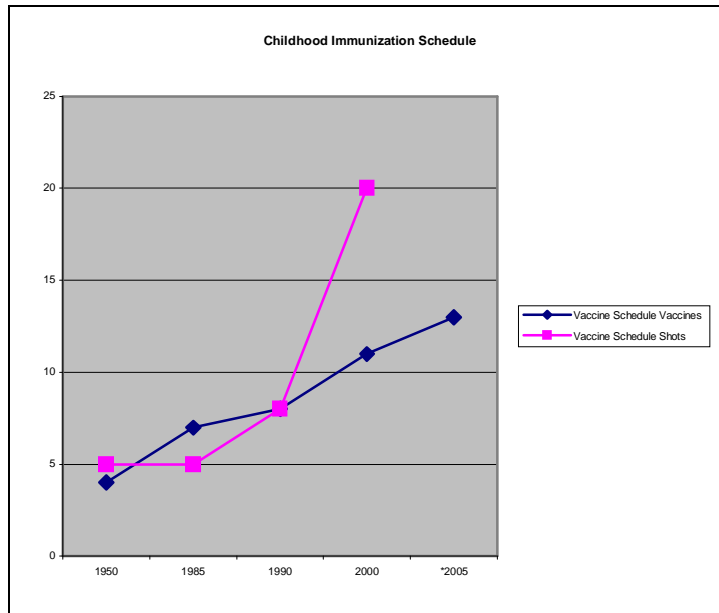
Vaccines have experienced steady growth in the last decade. In 1994, the global vaccine market was estimated at \$1 billion and increased to a sales level of \$4.8 billion in 2002. (VMO (2002b) and GVM (2001)) The market is expected to continue to expand at this pace into the next decade. The potential introduction of new vaccines and the development of safer or easily administered vaccines provide continued growth. The United States vaccine market grew 7.8% in 2001 to reach a value of \$1.48 billion in 2002. The market has grown at a rapid pace in the last five years in large part due to an emphasis on universal immunization coverage for children.



Vaccines administered during childhood make up a large share of the global market. In the United States the demand for childhood vaccines is determined both by the infant population and the Center for Disease Controls' (CDC) recommended schedule. Approximately 11,000 infants are born in the United States every day. While this provides a continual source of demand for vaccines, it has been very stable over the last decade. In fact, in the United States the infant population growth has been relatively steady for the last two decades. (CDC (2002b))



Most growth has been in the number of vaccines recommended by CDC, which has risen dramatically. In the 1950's only four vaccines were recommended: diphtheria, tetanus, pertussis and smallpox. Today the CDC recommended schedule includes nine vaccines, with more to be added by 2005.(CDC (2002a)) The recent introduction of Varicella zoster virus vaccines to the immunization schedule has contributed greatly to the vaccine market's growth. (VMO (2002a)) The growth in the number of recommended vaccines has increased not only the number of shots a child must receive, but also the number of doctor visits required to complete the immunization schedule. In response to this increase, several combination vaccines have been introduced.

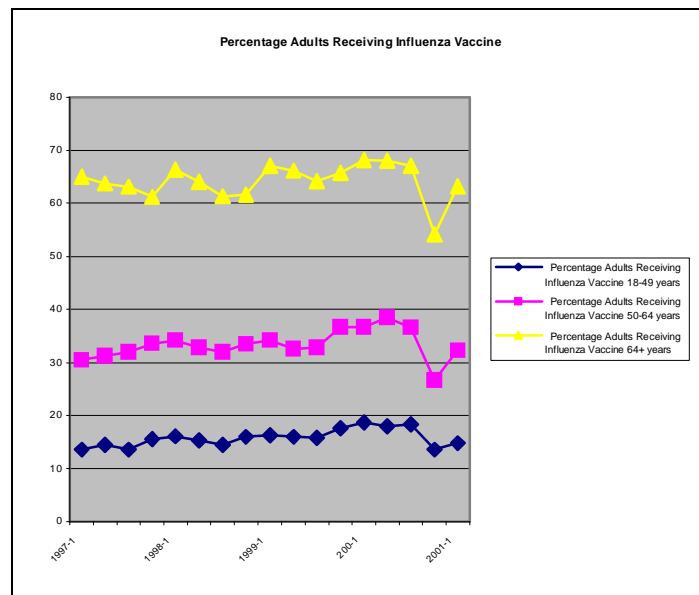


An additional source of growth in demand for childhood vaccines has been the implementation of the Childhood Immunization Initiative. Two primary goals of the program are that 90% of United States children should receive required immunizations by age two, along with the eradication of several childhood diseases. Immunization coverage rates in the United States have risen since the inception of the initiative. The program has met the 90% coverage goal for several vaccines. Further by 1996, three diseases, tetanus immunizations of children under age 15, and for the polio and mumps indicators, reached their elimination targets. (CII (1997))

Vaccine coverage in 2000 among children aged 19-35 months

DTP/DT/DTaP	Poliovirus	Hib	MMR	Hepatitis B	Varicella
94.1%	89.5%	93.4%	90.5%	90.3%	67.8%

While many vaccines are aimed at children there are several vaccines administered to adults. The CDC recommends that all adults receive the Diphtheria-Tetanus (DtaP) vaccine. Additionally, adults who have not been infected by the diseases and who have not been previously immunized should receive Varicella, MMR and Hepatitis B vaccines. Before 1999, the CDC recommended that adults over sixty-five receive the influenza vaccine. Currently the recommended age has been reduced to fifty, which has increased demand.(Vaccines for Adults (2002)) Those over sixty-five also should be immunized for pneumococcal. The hepatitis B vaccine is only recommended for adults who are at risk.



The CDC goal of 60% influenza vaccine among elderly Americans has been met. However, that goal will be raised to 90% in the year 2010. The current rate is below 70%. If the goal is met there will be an increase in demand for the influenza vaccine. Additional demand may also occur if the CDC takes action to combat the low rate of influenza vaccines among high-risk individuals.

Critical Issues: There has been relative steady growth in the total sales of vaccines. In the US the major growth occurred as a result of increases in dosages of specific basic childhood vaccines and the introduction of new childhood and adult vaccines. Basic childhood vaccines have a very predictable growth dependent upon annual birth rates. Markets for existing vaccines remain dwarfed by other pharmaceutical markets and as such are more likely candidates for exit than entry.

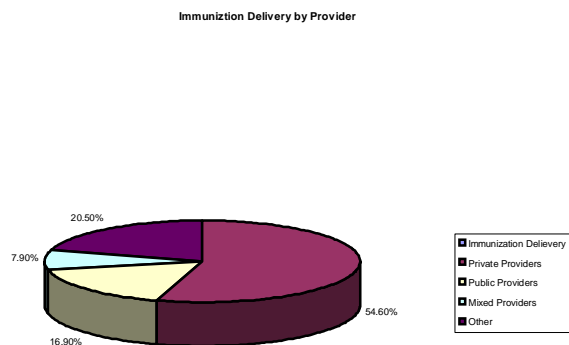
IV. VACCINE DELIVERY

In the past decade, the government has assumed a larger role in the purchase of vaccines. With the creation of the Vaccine for Children Program, the government has increased the number of vaccines it purchases. In 1985 only 15% of DTP vaccine was purchased by the public. That amount had risen to 56% in 1995. While the increased public purchases may have the benefit of increasing the number of children immunized, it also may affect the number of vaccine producers. The cost of privately purchased DTP in 1996 was \$5.54 per dose. If that same dose was purchased publicly, the cost would be a mere \$1.40. As the government assumes a greater role in the market, the average revenue per dose should fall. This may contribute to the already declining number of producers. (Grabowski and Vernon (1997))

The government's role is not the only factor reducing the average price per dose. The last decade has also seen an increase in the number of children enrolled in a HMO. Again, this may increase the number of children receiving immunizations. (Calling the Shots (2000)) However, HMOs also receive a discounted price for the vaccines they

purchase. It is believed that the discount provided to HMO is not as great as those given to publicly purchased vaccines. But the discount may add further pressure to lower vaccine prices and reduce the number of vaccine producers.

The vaccine industry also has changed in the location at which vaccines are administered. Increasingly children are receiving vaccines in their medical homes. Private insurance plays an important role in the administration of and payment for vaccines. Fifty-four percent of infants and 62% of children from 1 to 5 years of age are covered by private insurance. Approximately half of those policies cover immunizations. (Calling the Shots (2000)) Many states have enacted legislation to try to improve immunization coverage by requiring policies to provide coverage of immunizations. The growth of health maintenance organizations (HMO) has also increased immunization as almost all HMO's cover vaccines. In fact one of the measures of quality of an HMO used by some is the level of immunizations of their insured population. The number of individuals enrolled in HMOs has increased from 6 million in 1976 to approximately 67.5 million twenty years later. (Calling the Shots (2000))



The increasing number of children receiving vaccines from their primary care giver is in large part due to the creation of the Vaccines for Children Program (VFC). (Calling the Shots (2000))The VFC was created as part of the Children’s Immunization Initiative. The program focused on providing vaccination in a child’s medical home under the assumption that this would increase immunization rates. The program is a federal entitlement program that is administered by individual states. The VFC pays for and distributes vaccines to both public and private health providers. States may choose different methods of supplying the vaccines and different eligibility requirements. (Calling the Shots (2000), 16)

Vaccine Supply Policy – December 2000

Universal Policy	Public Vaccines Supplied for VFC and the Underinsured	Public Vaccines for VFC Only	Selected Public-Purchased Vaccine to ALL Private Providers
Alaska American Samoa Idaho Maine Massachusetts N. Mariana Island New Hampshire New Mexico North Carolina North Dakota Rhode Island Virgin Islands Washington	Arizona Florida Georgia Guam Houston Kentucky Maryland Michigan Minnesota Montana New York New York City Oklahoma Puerto Rico San Antonio South Carolina Texas Wyoming	Alabama Arkansas California Colorado Delaware District of Columbia Hawaii Indiana Iowa Kansas Louisiana Mississippi Missouri Nebraska New Jersey Ohio Oregon Pennsylvania Philadelphia Tennessee Utah Virginia	Chicago Connecticut Illinois Nevada South Dakota Vermont

		West Virginia Wisconsin	
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Source – Vaccine for Children Program

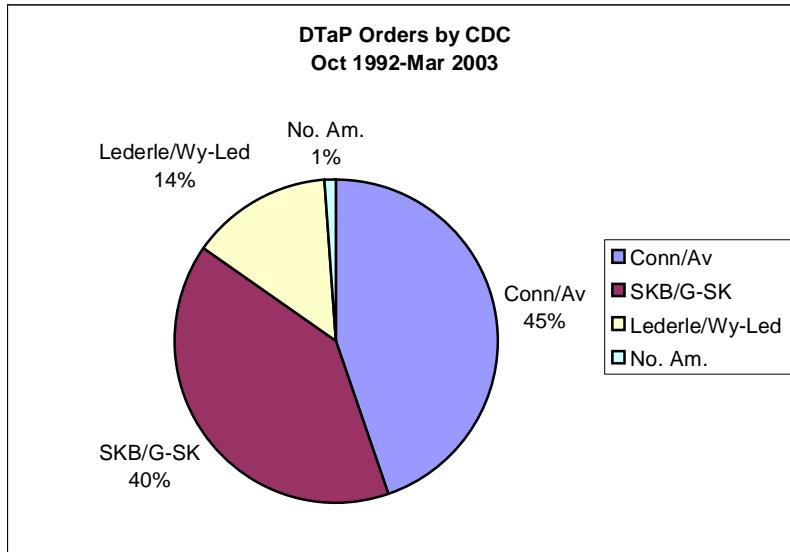
Approximately 35% of infants are immunized using VFC provided vaccines.

Health care providers enrolled in the VFC programs administer approximately 75% of the vaccines to school age children. The VFC has increased the amount of children who are able to have vaccinations administered in their medical home. A national survey found that 44% of providers who participated in the program referred uninsured patients to free clinics versus 90% who did not participate. (JAMA (1999))

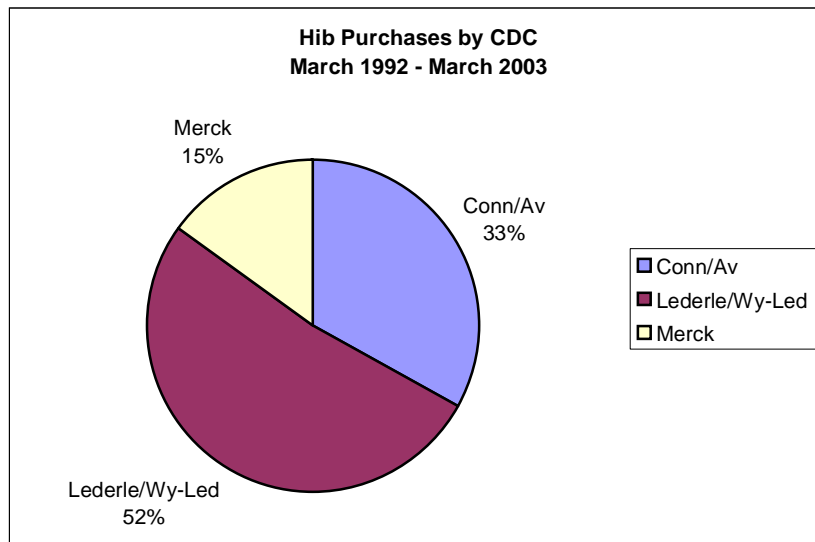
Additional supply of vaccines to the public is funded by Section 317 grants.

Section 317 was established in 1967 and was aimed at disadvantaged children. (Calling the Shots (2000)) Before the creation of the Vaccines for Children Program Section 317 grants were the major provider of public vaccines. In contrast to VCF, Section 317 grants cover both adult and childhood immunizations. Additionally, the funds can be used to support immunization delivery systems as well as purchase of vaccines.

The government makes approximately ½ of all vaccines purchases in the United States. Some of these purchases are by states. However, the federal government purchases the largest share. The following figures represent the universe of CDC purchases of DTaP and Hib vaccines over the period from 1992 – 2003.



Conn/AV: Connaught Laboratories Inc. changed to Aventis Pasteur Inc.
 Lederle/Wy-Led: Lederle-Praxis Co. changed to Wyeth-Lederle Vaccines
 SKB/G-SK: SmithKline Beecham changed to GlaxoSmithKline
 No. Am.: North American Vaccines

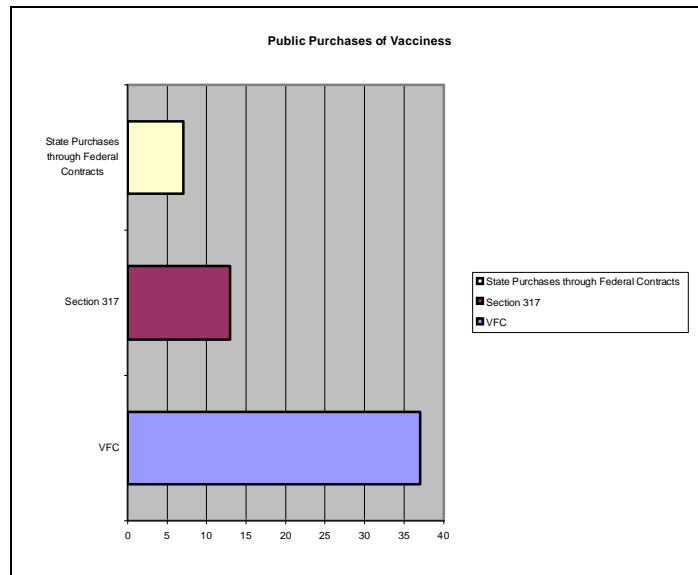


Conn/AV: Connaught Laboratories Inc. changed to Aventis Pasteur Inc.
 Lederle/Wy-Led: Lederle-Praxis Co. changed to Wyeth-Lederle Vaccines
 Merck: Merck Vaccine Division

The final source of public funding of U.S. vaccine purchases occurs at the state level. The amount of involvement depends upon the state. Twenty- four states purchase less than 10% of the vaccines administered in their state, whereas 10 states purchase 30%

or more. State funds generally are used to provide for vaccine delivery in public clinics.
(Calling the Shots (2000))

The increased number of vaccines purchased by the public and HMOs has increased the number of children immunized. However, the discounts both groups receive may be contributing to the exit of vaccine producers. The vaccine industry has continued to grow in the last decade. But, this is largely due to the introduction of new vaccines and vaccines targeted for adults.



International

Internationally, third parties purchase most vaccines. Volume is high in UNICEF, total sales revenue is in US and high income countries (see Grabowski and Vernon (1997) and Mercer (2002)) The majority of high volume purchases are made by the United Nations. These purchases are predominantly childhood vaccines for distribution via UNICEF to

lower income nations. Table VIII lists the current vaccines under contract by the UN, including the manufacturer.

Table VIII
UN List of Prequalified Vaccines
WHO List of Vaccines for Purchase by UN Agencies as of April 2002

PRODUCER	VACCINES
<u>Aventis Pasteur, Canada</u>	DTP, measles
<u>Aventis Pasteur, France</u>	BCG, DT, dT, DTP, OPV, TT, measles, MMR, Hib, yellow fever, meningococcal A + C
<u>Biken, Japan</u>	Measles
<u>Bio Farma, Indonesia</u>	DT, DTP, OPV, TT, TT filled in Uniject, measles
<u>Biomanguinhos, Brazil</u>	Yellow fever
Center for Genetic Engineering and Biotechnology, Cuba	Hepatitis B (recombinant)
<u>Cheil Jedang, Korea</u>	Hepatitis B (plasma derived)
<u>Chiron Behring, Germany</u>	DTP, Rabies
Chiron Vaccines, Italy	DTP, MMR (measles, mumps, rubella combination), MR (measles, rubella combination), OPV, measles, Hib
<u>CSL, Australia</u>	DT, DTP, TT
<u>GlaxoSmithKline, Belgium</u>	Hepatitis B, Hib, OPV, meningococcal A + C, DTP-Hep B, DTP-Hep B to be combined with Hib (pentavalent), measles, MMR
<u>GreenCross Vaccine Corporation, Korea</u>	Hepatitis B (recombinant)
<u>Human Co., Hungary</u>	DT, TT, Td
<u>Institut Pasteur Dakar, Senegal</u>	Yellow fever
Japan BCG	BCG
Lucky Goldstar, Korea	Hepatitis B (recombinant)
<u>Celltech Group plc. (formerly Medeva, U.K.)</u>	BCG, Yellow fever
<u>Merck and Co. Inc. USA</u>	Hepatitis B
National Center for Infectious and Parasitic Diseases, Intervax, Bulgaria	BCG
<u>SBL Vaccin AB, Sweden</u>	Inactivated oral cholera
Serum Institute of India	DT, dT, DTP, TT, MR, measles
<u>Statens Seruminstitut, Denmark</u>	BCG
Wyeth Lederle Vaccines and Pediatrics, USA	Hib

Critical Issues: A large and growing proportion of vaccines are purchased and distributed by public agencies in the US. Vaccines have a two-tiered pricing structure in the US, with government purchases priced large percentages below private purchases. In addition, sales to managed care entities have grow in the past decade. These entities also command a

discount from other private sales. As more sales are made at discounted prices the incentives for producers to remain in or enter vaccine markets declines.

V. VACCINE RESEARCH AND DEVELOPMENT

A concern voiced by some is that there has been a declining interest in investing in R&D to improve existing vaccines and discover vaccines directed at new indicators. In this section we provide a brief discussion of this issue. Vaccines have been available for over 200 years. It was almost a century after the smallpox vaccine was developed that a second vaccine was available. Few others were developed in the early twentieth century. (USVR (1997)) Today hundreds of vaccines are in various stages of development. Grabowski and Vernon (1997) reported that there were “285 vaccine R&D projects in progress (not including HIV vaccine efforts), of which 133 were already in clinical trials. (Grabowski and Vernon (1997), p. 11.) Mercer (2002) reported that number had increased to 350 R&D projects, 188 in pre-clinical phase and 158 in clinical trials in 2000. (Mercer (2002), no page).

Along with a change in the pace of development, the science used to create new vaccines is changing. Vaccine development has gone through several stages from weakened or killed microbes to new tissue culture techniques. Today scientists are using advanced genetic engineering to create new and safer vaccines. These new techniques have produced vaccines to fight Hepatitis B and Lyme disease. (GH (1998))

Much of the R&D projects are for the development of new vaccines, aimed at indications not currently targeted by a vaccine sold in the United States. Table IX presents a list of diseases where no vaccine protection exists as of yet. The last column is a rough indication of the relative importance of the particular disease versus the others in this table.

Table IX
Deaths from Diseases No Yet Preventable by Immunization

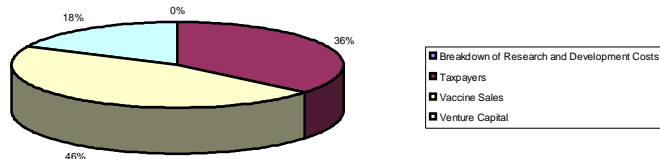
Diseases	Deaths (000)^a	%
AIDS	2285	27.47
Tuberculosis	1498	18.01
Malaria	1110	13.34
Pneumococcus ^b	1100	13.22
Rotavirus	800	9.62
<i>Shigella</i>	600	7.21
<i>Enterotoxigenic E. coli</i>	500	6.01
Respiratory syncytial virus ^c	160	1.92
Schistosomiasis ^d	150	1.80
Leishmaniasis	42	0.50
Trypanosomiasis	40	0.48
Chagas disease	17	0.20
Dengue	15	0.18
Leprosy	2	0.02
Total deaths	8319	100.0

Source: Kremer (2000)

Not all vaccine development is aimed at uncovered diseases. In fact, some of the development activity is aimed at vaccines that would be competitors to (or, perhaps, improvements upon) existing licensed vaccines in the United States. Appendix A presents a comprehensive list of these vaccines grouped by their status in reaching a level where they could be distributed in the United States.

The United States has been responsible for the discovery and development of two-thirds of the new vaccines in the last twenty years. The major contributors to vaccine research in the US are: various government agencies, academic institutions, four large companies (Wyeth-Lederle Biologics and Vaccine and Merck in the United States and SmithKline Beecham and Pasteur Merieux Connaught based in Europe) and smaller biotech firms. In 1997, \$1.4 billion was spent in the United States on vaccine research and

development. The costs of research and development are funded by taxpayers through government agencies, vaccine sales and venture capital.



The government plays a major role in vaccine development in the United States. The National Institutes of Health (NIH) is responsible for identifying and supporting development of potential vaccines. The Federal Drug Administration (FDA) oversees the regulatory process necessary to bring a new vaccine to market. Further, the Center for Disease Control (CDC) and the Department of Defense (DOD) have support roles. CDC's support role is significant since it is the largest single buyer and distributor of vaccines in the US. The US Agency for International Development (USAid) is also involved in a more limited role. The NIH conducts some internal research, however it plays a more extensive role by providing grants for academic institutions and health-related agencies. The DOD conducts its own research and supports research conducted at academic institutions. The DOD focuses primarily on indicators that would affect military personnel abroad and terrorism. The USAID grants fund directly in large parts to institutions in less developed countries.

Of the government agencies involved in funding vaccine research, the NIH has the most important role. The National Institute of Allergy and Infectious Diseases (NIAID) is the division of the NIH which primarily deals with vaccine research. The NIAID provides funding not only for basic vaccine research, but also focuses on vaccines that may be related to bioterrorism. In 2002, the NIAID budget was \$2.4 billion. In total the NIH is responsible for approximately a third of all vaccine research funding. (NIH Big Winner)

Pharmaceutical companies are also a major source of vaccine research and development. The National Vaccine Advisory Committee estimates that 46% of the \$1.4 billion spent on R&D in 1995 was financed by vaccines sales. (USVR (1997)) The market can be divided into large companies and small companies. Large companies were estimated to contribute 15-20% of sales, \$650 million, in 1995 to research and development. In contrast small companies receive their funding from venture capital. In 1995 small companies contributed \$250 million to vaccine research and development. (USVR (1997)) Small companies, while contributing a substantial amount of investment, are only responsible for 18% of all funding. This compares to 46% from large pharmaceutical companies.

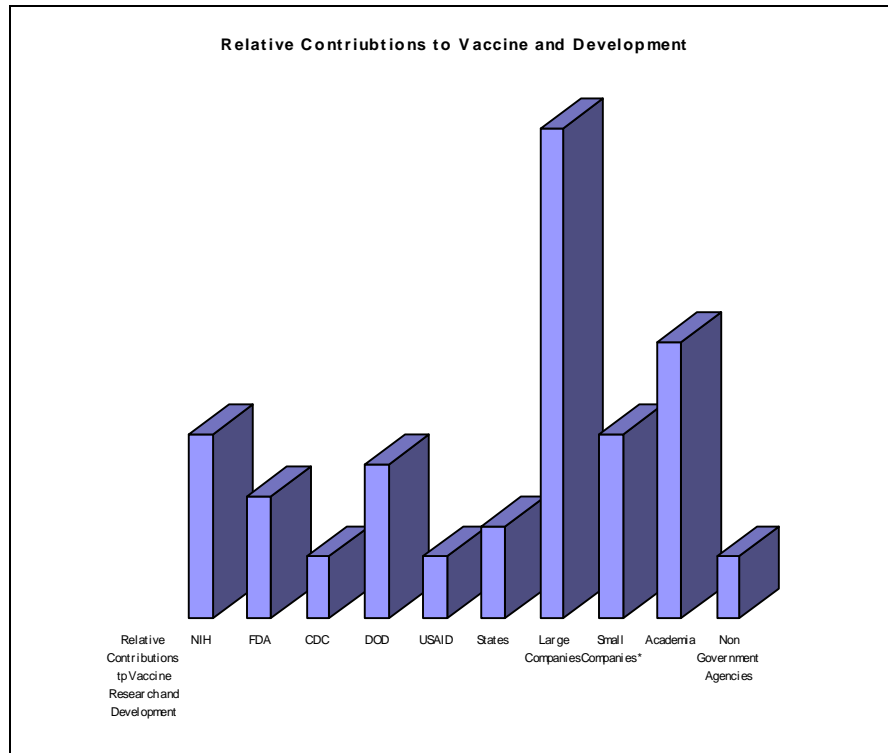
The large firm sector of the vaccine market consists of four major companies; Wyeth, Merck, GlaxoSmithKline and American Home Products. (NVAC). In contrast, there are many small biotechnology firms involved in vaccine research. These firms range in size from 36 employees (Antex Biologics, Inc.) to over 1600 employees (Immunex Corporation). The firm sales also have a wide range varying from almost \$1 billion (Immunex Corporation) to half a million dollars (AVAX Technologies, Inc.) The small

size of these firms can lead to enormous increases in sales. Antex Biologics experienced 200% sales growth in 2001.

Small biotechnology companies are distinct in funding, organization and interests. While all of the technology firms are involved in developing more than one drug, the areas of research vary. Some firms focus solely on vaccine research while other focus on a certain type of disease. Some of the biotechnology firms receive funding from the government. For example, Antex Biologics receive funding from the Department of Defense for trials of a potential vaccine against diarrhea and gastroenteritis. Other firms, are subsidiaries of larger pharmaceutical companies or may be partially owned by another firm. Immunex is a subsidiary of Amgen and Baxter owns about 20% of Acambis plc.

(Business 2.0)

Pharmaceutical companies respond to market forces and generally research vaccines that have potential for large revenues. This excludes many diseases, such as malaria, which afflict a disproportionate amount of the world's poor. In 2000, The Global Alliance for Vaccines and Immunizations (GAVI) was founded in part to respond to the need for vaccines in developing countries. GAVI is also interested in developing better technologies to administer vaccines as many health care workers in developing countries work in difficult environments. (GAVI website)



One of the major areas of recent research is vaccines for sexually transmitted diseases (STDs) and vaccines that can be effective in children. Extensive effort has been focused on finding a vaccine for HIV. Many health officials believe a vaccine is essential to stop the worldwide spread of the disease. Small human trials are being conducted by several pharmaceutical companies.(19)

While there has been no production of an effective HIV vaccine, scientists have learned a great deal about how the immune system works. This knowledge has spurred research on vaccines for various forms of cancer. Currently in the United States, there are over 150 vaccines in different stages of development. Three cancer vaccines are currently approved in other countries. The market for cancer vaccines is projected to grow by over 100% through 2007.

Along with developing new vaccines, research is being conducted to discover new methods of administering vaccines, such as, the development of a nasal spray form of the

influenza vaccine. (Inoculate (2001)) Vaccines are considered to be less profitable than many other pharmaceutical products. This might lead to less funding for vaccine research and development. In 2000, \$26.4 billion was spent world-wide for pharmaceutical research. Of that money \$22.4 billion was spent in the United States. While the absolute figure for pharmaceutical spending is much larger, the market for all pharmaceutical is much larger than the market for vaccines. General pharmaceutical research spending was approximately 20% of all sales. This is roughly the same percentage of vaccine sales that is spent for vaccine research.

Further, the government also plays a large role in all pharmaceutical research. The NIH allocates about 60% of its funds to basic research, with the remainder going to clinical trial. While it is hard to estimate the contribution of the basic research funds to pharmaceutical R& D, an estimate of the share for direct involvement can be obtained. In 1988, the NIIH contributed an estimated 14% of all funding for preclinical pharmaceutical R& D. Eleven percent of clinical trial costs were funding by the NIH in that same time period. (CRS-19)

Critical Issues: The level of R&D expenditures generated by private funding appears to be stable and may even have increased in very recent years. Most of the R&D is directed to projects whose purpose is to discover vaccines against new indicators and combination vaccines. While discoveries in either category may increase entry, those of the former variety create new markets and those of the latter tend to replace existing production. These are positive outcomes but do not generally increase the number of players in any specific vaccine market.

VI. REASONS FOR SMALL NUMBER OF SUPPLIERS

The purpose of this section is to attempt to use concepts of economic analysis along with antidotal evidence to tie the information presented above to possible reasons for the existence of small numbers of suppliers in most vaccine markets. The tables presented in the prior sections of this paper present a somewhat confusing picture. The total list of vaccine producers is long and there is significant entry of firms producing or testing new vaccines. On the other hand, most of the vaccines being produced are not substitutable and are effective against only one indicator. Similarly, combination vaccines have only limited substitution possibilities with single indicator vaccines or other combination vaccines. In fact they often replace rather than substitute for existing vaccines. The level of substitution also may be limited among producers because often the same company that produces the combination vaccine produces the individual indicator ingredients. The result is that many vaccines distributed in the US have only one or a very small number of producers. We showed in Table VI that several childhood vaccines had a single source of supply in the US. Furthermore, most US producers provide only limited supply to the international market from their US plants. Similarly, foreign producers export only limited supply to the US market from their foreign plants. It has been estimated that over 60% of DTP is produced in the same country in which it is used. (Vaccine Demand and Supply) Clearly the limited number of suppliers and the recent withdrawal of some from certain markets is a significant factor in the recent shortages

A number of reasons have been espoused for the small number of suppliers in the US childhood vaccine markets. These generally are encompassed within various aspects of the cost structure of the vaccine production relative to the size of the US market. Grabowski

and Vernon break this into four factors: regulation costs, liability costs, R & D and low risk adjusted returns relative other pharmaceutical products. (Grabowski and Vernon (1997), 7) In this section we will discuss the cost structure of vaccine production. This must be qualified with the statement that we have no cost data that would permit a detailed estimation of cost functions. Therefore, this discussion is necessarily based on limited information reported by others; some of the results relate specifically to vaccine production; other information is developed from similarities of vaccine production to the production of other pharmaceuticals; some information is totally anecdotal in nature. Finally, some of the conjectures we make are based on statements by industry representatives.

Vaccines Production Has High Fixed Costs

The costs in the pharmaceutical industry are comprised of very high fixed costs. Total costs include R & D, costs related to the regulatory approval process, ongoing regulatory costs, plant costs including depreciation, marketing costs, variable labor, production, equipment and supplies, and liability costs. Grabowski and Vernon estimated that the R & D and regulatory approval process generated an average of 11 years of negative cash flow in the “new chemical entities (NCE) introduced in the US pharmaceutical industry over the 1980-1984 period. DiMassi et al (1991) estimated mean out of pocket cost of successful NCEs to be \$32 million in 1987 dollars.(p.17) If discovery, clinical testing and failure costs are included DiMassi et al estimate average out of pocket costs to be \$115 million (1987) for the NCEs in their survey. Capitalizing time and interest costs into these estimates results in an estimated cost of \$231 million

(1987).(p. 20) Grabowski and Vernon (1997) indicate that this is over \$300 million in 1997 dollars for the introduction of a NEC.

The estimates of bringing a NCE to market are well within the IOM estimates of \$20-50 million for bringing eight vaccines to market. (Reported in Grabowski and Vernon (1997), p. 20) There are at least two ways in which the cost of developing and bringing a vaccine to market differ from that of the pharmaceuticals. First, the success rates for vaccines may be greater than for pharmaceuticals. However, two of the studies projected high success rates while many of the biologics were still subject to development and testing and were not yet marketable. (Grabowski and Vernon (1997), p. 20-21) Grabowski and Vernon conclude that overall “there is some basis for expecting that recombinant vaccines are characterized by higher success rates and faster development times as compared with new chemical entities.” (p.25.)

Vaccines require both a product license (PLA) and an establishment license (ELA) while NCEs require only the former. The ELA certifies that the facilities, equipment and personnel involved in the manufacturing process meet FDA standards and Good Manufacturing Practices. In addition, once in production, each “batch” must be tested and approved prior to release. This batch approval is not required of pharmaceuticals. As a part of the initial approval process the FDA recommends that the phase III clinical trials be produced in a commercial production facility that will be used for commercial production if the biologic is approved. Grabowski and Vernon report that this requires an investment often greater than \$30 million in plant before the product is approved. (p. 27) Bader estimates that this could result in the cost of bringing a biologic to market being as much as \$25 million more than that of a pharmaceutical. (Reported in Grabowski and Vernon

(1997)) In addition to requiring that this investment be made up front, production facilities for biologics tend to be more capital intensive than those of NCEs. The combination of these factors results in many vaccines not only being produced by one company but also being produced in one large-scale plant.

The production process for vaccines, once approved, also is characterized as having high fixed cost relative to variable costs. Mercer (2002) states that fixed production costs, exclusive of up-front R & D and sales labor, comprise 60% of total production costs.

(Mercer (2002)) These are costs that are totally invariant to changes in output. The major fixed production costs are personal devoted to quality assurance activities, administrative labor, depreciation, and other manufacturing overhead. Industry representatives indicated that in recent years QA employees have been growing relative to production employees as a result of increased regulatory requirements. (Statements at May IOM meeting in Washington)

Mercer (2002) estimates that semi variable costs comprise 25% of total costs excluding R & D and sales labor. Semi variable costs are batch costs that are constant per batch regardless of the number of batches. (Mercer, 2002) Specific examples of batch costs are labor for production and testing and animals used for testing.

The remaining variable costs account for 15% of total costs. Examples of variable costs are vials, stoppers, labels, packaging and in-source components.

Critical Issue: Vaccine production involves very large front loaded R&D and regulatory costs, the latter of which continue into the ongoing production process. The production process also is very capital intensive and involves semi fixed costs due to the “batch”

process. These high fixed costs generate a situation in which marginal cost are below average costs, and probably significantly lower than average costs throughout the relevant range of production output.

Costs and Entry

Our focus now turns to the ties between the cost structure of the vaccine industry and entry and exit. The vaccine industry clearly exhibits economies of scale in the sense that costs per dose are extremely sensitive to volume. Therefore, it is not surprising that most vaccine markets seem to have a common life cycle. The tables presented earlier in this report reveal that a substantial number of firms generally are involved in the early stages of discovery and development of new vaccine products. More than one firm usually has been licensed to produce most vaccines in the early period following regulatory approval. As the markets for specific vaccines mature, the number of firms continuing to hold licenses declines and the number marketing the vaccines often declines to one firm.

Various scenarios can explain the mechanics of the decline in the number of firms in markets characterized with costs that decline substantially with increases in volume. Ideal to an analysis of this nature would be the availability of actual producer cost data that would enable the estimation of cost functions from which minimum efficient scale could be determined. Then it might be possible to determine with reliable levels of statistical confidence the number of firms the vaccine markets can efficiently accommodate. We state again that we do not have empirical data to validate the scenarios we describe. However, market outcomes provide validation of some of our conjectures. First, it is construed by many researchers in this area that domestic vaccine markets (particularly the US market for childhood vaccines) are small relative to the extent of economies of scale.

Let us assume that all firms producing a vaccine for a specific indicator have equal market shares. Any one firm that is able to increase doses sold, can price the product below that of the now smaller producer, thereby further increasing its ability to reduce price and further enhance market share. Examples of conditions that might permit a firm to increase market share include superior product quality and delivery systems. Alternatively, a firm may preemptively reduce prices hoping to gain first mover advantages.

Cost conditions we have described are consistent with there being a low probability of entry of new firms in established vaccine markets. Even if new firms can avoid some of the front loaded R & D costs, existing producers can price very low because MC are extremely low relative to AC. Obviously existing firms have an incentive to adjust prices to deter entry. Therefore, even in the absence of data to conduct an extensive cost analysis, there is ample antidotal evidence along with actual market outcomes, to draw the conclusion that economies of scale resulting from very high front loaded costs and high production fixed costs provide a substantial barrier to entry of new firms and a pricing behavior that encourages exit as soon as one of the small number of producers establishes a clear market lead.

Critical Issues: Even though multiple firms may be involved in the production of some specific vaccines early in the history of the vaccine, the cost structures of vaccine markets supports a process in which: entry of new firms into existing markets is not likely and exit of existing firms is likely, with a life cycle that results in monopoly or near monopoly markets.

Market Size, Growth, and Returns: Vaccines v. Pharmaceuticals

An important question to address as we continue our focus on costs and single and dual producer markets, is why so many vaccine product markets have a life cycle of gravitating to a very small number of producers, many as few as one, while the same behavior does not appear to be as likely in markets for other pharmaceutical product. Grabowski and Vernon report that costs of getting products to market are similar for both types of products and with new recombinant development processes may actually be lower for vaccines. (Grabowski and Vernon (1997), 24). We believe there are two very important differences that explain the different market structures: market size and pricing behavior.

a. Market Size and Growth

Mercer (2002) estimates the global market for vaccines (childhood and adult) to be \$6B and growing at approximately 10% per year since 1992. (Mercer, 2002). Adult vaccines account for less than 30% of the global market while basic and new pediatric vaccines account for the remainder. The US market is small. In fact total sales of childhood vaccines in the US are surpassed by the sales of a single major pharmaceutical product such as *Prilosec*. Mercer (2002) contends that US multinationals have high costs relative to European multinationals because the former produce in the vicinity of 100 million doses while the latter have average production of over 1 billion doses.

Growth in specific vaccine markets could permit the emergence or retention of multiple producers. However, growth in total vaccine revenues in the 1990's has be

modest. Growth in basic childhood vaccines has been almost nonexistent. In the US, 72% of the growth in total revenues resulted from the introduction of new products and 10% from the increase in the MMR dosage from 1990-95. (Mercer (1995), p.21) Globally, a significant proportion of the growth during the entire decade of the 1990's was the result of the worldwide effort to eradicate polio. The remainder of the market grew as an annual rate of approximately 1%. (Mercer (2002)). Thus, new products have been generating growth and new entry, but new products are likely to go through the same product cycle as more basic vaccines. Even where multiple firms enter the market we should expect to see a movement toward one or two producer markets over time short of unforeseen changes in technology or the globalization of vaccine markets.

Vaccine producers tend to focus more on domestic markets than global markets. As we stated earlier, 60% of DTP was distributed in the country in which it was produced. The similar ratio may be lower for some other vaccines, but for various reasons a real global market does not exist. It is conjectured by vaccine experts that there are two reasons foreign producers are not more active in the US market. First, the costs of obtaining regulatory approval are considerably higher in the US than in European countries. Second, companies distributing vaccines in the US have been subject to very high liability costs. On the first point, regulatory costs have been increasing in the US as a result of various factors including increases in the number of required clinical trials and the need for more QA personnel. (Statements by industry representatives, May 2002). It also has been conjectured industry representatives that regulatory costs have increased as a result of an increase in the number of regulatory warning letters issued by FDA. However,

information provided on the FDA website rate of issuance of warning letters over very long periods of time.

On the second point, many industry experts credit liability costs as a primary reason for firms exiting from the vaccine markets in the 1970's and 1980's. (Grabowski and Vernon (1997), 8-9). The passage of the National Childhood Vaccine Injury Compensation Act in 1986 greatly reduced liability costs related to childhood vaccines. The Act provides the development of the Vaccine Injury Compensation Trust Fund, revenues being generated from an excise tax per dosage on DTP, MMR and OPV. The Fund provides no-fault compensation for children harmed by certain children vaccines. However, the NCVICA only applies to certain childhood vaccines and does not cover 100% of the costs incurred even for childhood vaccines. Industry representatives state that expenses related to liabilities remains a problem even though these costs have been reduced. (Statements by industry representatives, May 2002)

US companies do not more actively distribute vaccines in foreign countries for another set of reasons. First, it is stated in the Mercer (2002) that US multinational firms have higher costs than those of Europeans because of the higher labor cost in the US and the small size of the US market. Clearly, production facilities in the US could be expanded, but in Mercer (1995), it was stated that it is very costly to resize plants to serve new markets. (Mercer (1995)-p.9.)

Second, vaccine prices in other high-income countries are considerably below the prices charged to private and public purchasers in the US. The US has had a multi tiered pricing structure for many years that we described earlier. Prices at which vaccines are sold to international organizations such as the UNICEF, for distribution to lower income

countries, are even lower than the price sold to public purchasers in the US. US industry experts have voiced concern that Congress will put political pressure on US firms to reduce their prices in the US further if they sell to other countries at prices considerably below those charged in the US. This would further reduce returns to vaccine investments relative to other pharmaceuticals.

Critical Issues: Most growth in vaccine markets is the result of CDC requiring more dosages of existing vaccines and the discovery of new vaccines, factors that do not lead to optimistic conclusions about the result of entry into existing markets. Also, due to regulatory and political issues, currently only limited vaccines are exported across international borders.

b. Pricing and Returns on Investment

The cost structure we have just described provides evidence as to why there are so few producers of each vaccine. However, this does not speak to the ultimate “bottom line” issue discussed by Grabowski and Vernon (1997) and others. They contend that entry and retention in the vaccine markets is difficult because returns on investment are less than on other pharmaceuticals. While this is partly due to the size of the market, it is largely due to the pricing structure of vaccines. Mercer (1995) provides estimates of contribution to margin of vaccines compared to pharmaceuticals. While they find substantial difference in other aspects of the cost structures, they find contribution to margins to be very similar: 44% for vaccines and 46 % for pharmaceuticals. However, vaccine production is more capital intensive reducing the return on capital investment for vaccines.

According to Mercer (1995), contribution to margin varies greatly across different vaccine products and even more so between private and public sales. All comparisons include contribution to R&D, interest, taxes and earnings. Monopoly products (MMR and OPV) have the highest estimated contribution. Next highest are new products. Mercer estimates the contribution generated by private sales of MMR/OVP to be \$8.40 compared to \$2.90 on sales to public purchasers. This is a difference of almost three fold even after accounting for the much higher cost of distribution to private purchasers.

Changes in purchase patterns that we have already described can have a major negative impact on contribution to margin raise concern about the viability of maintaining multiple producers in vaccine markets. Grabowski and Vernon report relatively steady increases in the proportion of DTP, MMR and OPV being publicly purchased. (Grabowski and Vernon (1997), Table 1-2, p 4.) The percentage of publicly purchased doses of children's vaccines took a substantial jump in 1995, the first full year of the Vaccines for Children entitlement program.

The private purchasers are changing as well. The growth of managed care organizations along with the commensurate increase in their purchasing power has resulted in a growing segment of the private purchasers receiving discounts along with the public purchasers. Little is know about the extent of these discounts that are received by managed care purchasers, but it is believed to be below the discount provided to public purchasers.

The impact of growth in the share of vaccines purchased by public purchasers and private purchasers receiving discounts has a very direct impact on entry into vaccine markets. Entry into existing and new vaccine markets is very dependent upon expenditures on R&D to develop new vaccine products and production processes. To date,

and contrary to expectations, this may not be happening. Mercer (2002) reports that in 2000, Merck, Wyeth, GSK, Aventis and Chiron spent in excess of \$750 million on R&D, a “significant increase, both in absolute terms and as a percentage of sales, over the level of R&D investment in 1992.” (Mercer, 2002). Mercer (2002) speculates that operating margins of the large multi nationals is higher than it was in 1992 and that the higher returns result from lower liability costs and concentrating R&D investment in areas where there is demand from high-income buyers including the sale of “adult/travel, proprietary and enhanced pediatric products.” (Mercer, 2002) This is consistent with the information we provided in Appendix A. Grabowski and Vernon provide evidence that supports this activity as well, stating that there were 285 R&D projects in operation in 1996, of which 133 were in the phase of clinical trials. (Grabowski and Vernon (1997), p. 10-12). These expenditures have had a positive impact on outcomes. From 1997-1999, 17 new US vaccine licenses were granted compared to 8 between 1990 and 1992.

Another change that has occurred that could have a positive impact on entry into vaccine markets is the increase in R&D being carried out in small biotech firms. Their involvement is generating numerous R&D activities. To the extent they are successful in the discovery stage, they frequently sell their product to a large pharmaceutical firm because they lack the resources to finance the testing stages. Where the discovery is developed through testing by the smaller biotech firm, the production and distribution of the product is often licensed to one of the larger pharmaceutical companies.

The long run impact of the emergence of the biotech firms on the structure of the vaccine markets is difficult to predict. Also, there is an increase in the number of substances involved in the production of vaccines that are patented. This will change the

cost structure of producing vaccines. “Hep B has 14 different patents and a number of organizations with royalty rights.” (Mercer (2002), p 27) Royalty payments have been estimated to be as much as 15% of sales for this vaccine. Similar payments for Hib and DTaP are estimated to be in the range of 4-6% of sales. (Mercer (2002) p. 27.) There must be a tradeoff between the increased royalty costs and the reduction in front loaded and possibly other capital costs. However, once again only antidotal evidence is available, and little can be said about the ultimate impact.

Critical Issues: Multi-tiered pricing exists in vaccine markets in the US with public purchasers receiving large discounts. In the last decade there has been growth in purchases by large managed care organizations that also receive discounts. Contribution to margins from sales to private purchasers is a multiple of that from sales to public purchasers. Growth in public and managed care purchases as a percent of total, reduces incentives for entry (this is true of firms selling across international boundaries, as well), and R&D and increased incentives for firms to exit existing markets.

VII SUMMARY AND CONCLUDING COMMENTS

We believe the critical issues in the industrial organization of vaccine markets can be summarized as follows:

Economies of Scale and Market Structure

- Vaccine markets are small relative to the markets for many other pharmaceutical products.
- Vaccine markets generally rely heavily on domestic production and supply.

- Most of the basic childhood vaccines are produced by single suppliers and many of the newer vaccines are produced by only 1, 2 or 3 suppliers.
- There are very substantial economies of scale in the production of vaccines as a result of: fixed costs emanating from front loaded R&D and regulatory costs; ongoing fixed and semi fixed costs resulting from ongoing regulatory and QA costs; and capital intensive production processes relative to other pharmaceuticals.

Conclusion 1: These cost conditions are consistent with monopoly near monopoly markets. Furthermore, we predict that new vaccines will follow a market cycle of the mature markets for basic childhood vaccines. Numerous firms may be involved in the development process, which can be characterized as a race to be first. Multiple firms may be producing and distributing a vaccine initially. However, there are many more incentives for exit of existing firms than for entry of new firms when market size is limited and MC are significantly lower than AC and continue to decline with increased output. There is likely to be gravitation to monopolies in many of these markets, or a winner take all game played in these markets.

Pricing and Market Structure

- There is a two or three tier pricing structure for vaccines in the US.
- Contribution to R&D and other overhead is generally 3 or more times greater for sales to private distributors than to public and managed care distributors, who receive large discounts.
- The share of the market distributed through public and managed care purchasers is increasing.

Conclusion 2: Lower returns in vaccine markets relative to those of other pharmaceuticals have long been given as an explanation for exit in vaccine markets that results in monopoly or near monopoly markets. Growth in the segment of the market receiving large price discounts will further increase incentives for exit and reduce incentives for entry.

Conclusion 3: Almost half of the funds to support R&D to improve existing vaccines and discover new ones come from sales revenues. A reduction in contribution to R&D and other overhead resulting from increased share of the markets receiving discounts will reduce incentives to invest in R&D. This will result in less entry and new product development, and possibly more single producer markets.

Market Structure and Supply Interruptions

- There are many reasons for supply interruptions, but when they occur in markets with one supplier there is no one to make up the shortage. When they occur in as a result of an action of one firm in a market with a small number of producers, it is very difficult for remaining producers to expand output rapidly due to the “batch” production and regulation process.

Conclusion 4: This conclusion responds to the question of what is the likelihood of changes in the market to increase the number of firms in a perceptible manner to impact the shortage problems. Three factors that address this question are size of market, regulation and technology. Markets may be expanded to be more global in nature but data are not available to permit estimation of the number of firms that could be supported in a more global market. Also, more global and therefore more competitive markets will lead to reductions in prices, lower contributions to R&D and ultimately lower expenditures on R&D. Methods may be found to reduce front loaded and ongoing regulatory costs, but

while beneficial are not likely to have a major impact on numbers of firms that can be supported in domestic markets unless these changes also lead to more global markets. Finally, new technologies maybe created to lower costs. We currently are in such a world with biotech expansion but this new technology has yet to have a major impact on costs that would greatly change the structure of vaccine markets.

REFERENCES

- Arnould, Richard and Larry DeBrock (1993), "Equilibrium Outcomes in Vaccine Markets and the Implications for Policy Initiatives," in Mark Pauly, et.al. ed., *Supplying Vaccines: An Economic Analysis of Critical Issues*, IOS Press, London, 1995.
- Brichacek, Andra (2001), "Vaccine Worries," *Pharmaceutical Executive*, v21(WHO (2002)) March 2001, pp. 37.
- Calling the Shots* (2000). Washington, D.C.: Institute of Medicine.
- Cancer (2001), "Cancer Vaccine Markets Set to Explode Upon Commercialization of New Drugs, Says Frost & Sullivan," [online document] www.enviis.org.za/news%20bulletin/cancer_vaccine.htm.
- CDC (2002a), *Recommended Childhood Immunization Schedule*. [online document] www.cdc.gov/nip/recs/child-schedule.htm#Printable.
- CDC (2002b), "Percentage of adults aged 18 years and older who received influenza vaccines during the past 12 months," [online document] <http://www.cdc.gov/nchs/data/nhis/measure04.pdf>.
- CII (1997), "Facts About the Childhood Immunization Initiative" [online document] www.cdc.gov/od/oc/media/fact/cii.htm.
- DeBrock, Larry and Henry Grabowski (1985) "Economic Aspects of Vaccine Innovation and Manufacturing," Chapter 4, in *Vaccine Supply and Innovation*, National Academy Press: Washington, D.C., 1985, pp. 45-64.
- Dove, Alan (2001), "Report predicts burgeoning vaccine markets," *Nature*, v7(8) August 2001, pp 877.
- GH (1998), "Global Health: the United States Response to Infectious Diseases," [online document] www.niaid.nih.gov/director/congress/1998/0303/default.htm.
- Grabowski, Henry G. and John M. Vernon (1997) *The Search for New Vaccines: The Effects of the Vaccines for Children Program*, AEI Press, Washington, D.C., 1997..
- GVM (2001) "The Global Vaccines Market: Poised for Take-Off" [online document] www.inpharm.com/intelligence/frost090901.html.
- Inoculate (2001) "How can vaccine companies inoculate themselves?" [online document] www.inpharm.com/intelligence/datamonitor051101.html.
- JAMA (1999), "Strategies to Sustain Success in Childhood Immunizations," *JAMA*, v282(4) July 28, 1999.

- Kremer, Michael (2000), "Creating Markets for New Vaccines Part II: Design Issues", NBER Working Paper #7717, May 2000.
- Mercer Management Consulting (1995), *Report on the United States Vaccine Industry*, Commissioned by the Department of Health and Human Services, June 14, 1995.
- Mercer Management Consulting (2002), *Lessons Learned: New Procurement Strategies for Vaccines*, Final Report to the GAVI Board, June 28, 2002,
- MMWR (2000), "National, State, and Urban Area Vaccination Coverage Levels Among Children Aged 19—35 Months – United States, 2000." *Morbidity and Mortality Weekly Report* 50(30): 637-641.
- National Vaccine Advisory Committee, *United States Vaccine Research: A Delicate Fabric of Public and Private Collaboration*, American Academy of Pediatrics, 1997.
- UNICEF, *Vaccines for Children: Supply at Risk*. Hitt, Emma (2002), "Poor sales trigger vaccine withdrawal," *Nature*, v8(4) April 2002, pp311-312.
- USVR (1997), "United States Vaccine Research: A Delicate Fabric of Public and Private Collaboration" [online document] www.cdc.gov/od/nvpo/delfab.pdf.
- Vaccine Distribution Policy (2000) [online document] http://www.cdc.gov/nip/vfc/ImmunizationProject/Vac_Distrib_WebInfo.htm.
- Vaccines for Adults (2002) [online document] <http://vaccine.chop.edu/adults.shtml>.
- VMO (2002a), "United States – Vaccines Market Overview" [online document] <http://www.datamonitor.com/~46acac741fa04cde83e322b05496fce2~/all/capsules/markets/product.asp?pid=42C2A787-B5E7-4660-BB04-7BFAFDB503B2>.
- VMO (2002b) Global – Vaccines Market Overview [online document] <http://www.datamonitor.com/~46acac741fa04cde83e322b05496fce2~/all/capsules/markets/product.asp?pid=DCA5E7F3-2CCF-4A14-9B79-DA9694A9058A>.
- WHO (2002) *Immunization Profile – United States of America*. [online document] www.who.int/vaccines/GlobalSummary/Immunizations/CountryProfileResult.cfm.

Appendix A

Table X
Worldwide Vaccines Under Development, by Status of U.S. Approval Process

Status	Company	Country Name	Generic name
Phase I	ACAMBIS	UNITED KINGDOM	smallpox virus vaccine
	ACAMBIS (PEPTIDE THERAPEUTICS)	UNITED KINGDOM	influenza vaccine, mucosal
	ACAMBIS (PEPTIDE THERAPEUTICS)	UNITED KINGDOM	tetanus vaccine
	ACAMBIS (PEPTIDE THERAPEUTICS)	UNITED KINGDOM	e. coli vaccine
	AIXLIE PHARMACEUTICALS	UNITED STATES	cancer vaccine
	ALPHAVAX	UNITED STATES	AIDS vaccine
	ANTEX BIOLOGICS	UNITED STATES	shigella vaccine
	ANTEX BIOLOGICS (MICROCARB)	UNITED STATES	chlamydia trachomatis vaccine
	ANTIGENICS, INC.	UNITED STATES	HSP vaccine
	ANTIGENICS, INC.	UNITED STATES	HSPPC-96, pathogen-derived
	ANTIGENICS, INC.	UNITED STATES	AG-702, AG-02
	ANTISOMA	UNITED KINGDOM	FAB-2 HMF-1/CITC-DTPA CHELATE
	ASTRALIS	UNITED KINGDOM	
	AUSTRALIAN CANCER TECHNOLOGY	AUSTRALIA	Pentrix
	AVANT IMMUNOTHERAPEUTICS INC.	UNITED STATES	cholera vaccine
	AVENTIS (AVENTIS PASTEUR)	FRANCE	cancer vaccine, IL-2
	AVENTIS (AVENTIS PASTEUR)	FRANCE	HIV vaccine
	AVENTIS (AVENTIS PASTEUR)	FRANCE	HIV vaccine
	AVENTIS (AVENTIS PASTEUR)	FRANCE	meningitis vaccine
	AVENTIS (AVENTIS PASTEUR)	FRANCE	meningococcal A/C vaccine
	AVENTIS (AVENTIS PASTEUR)	FRANCE	meningitis B vaccine, transferrin binding protein
	AVENTIS (AVENTIS PASTEUR)	FRANCE	rabies vaccine
	AVENTIS (PASTEUR MERIEUX CONNAUGHT)	FRANCE	
	BARR LABORATORIES	UNITED STATES	adenovirus vaccine
	BAXTER INTERNATIONAL (BAXTER HYLAND IMMUNO)	UNITED STATES	influenza B vaccine
	BAXTER INTERNATIONAL (IMMUNO)	UNITED STATES	lyme disease vaccine
	BAXTER INTERNATIONAL (NORTH AMERICAN VACCINE)	UNITED STATES	meningitis B vaccine
	BAXTER INTERNATIONAL (NORTH AMERICAN VACCINE)	UNITED STATES	meningococcal B/C vaccine
	BAXTER INTERNATIONAL (NORTH AMERICAN VACCINE)	UNITED STATES	DTaP Hib vaccine
	BAXTER INTERNATIONAL (NORTH AMERICAN VACCINE)	UNITED STATES	TdaP vaccine
	BAXTER INTERNATIONAL (NORTH AMERICAN VACCINE)	UNITED STATES	haemophilus type B vaccine
	BIOSANTE PHARMACEUTICALS	UNITED STATES	chlamydia vaccine
	BIOSANTE PHARMACEUTICALS	UNITED STATES	h. pylori vaccine
	BIOSANTE PHARMACEUTICALS	UNITED STATES	streptococcal vaccine
	BIOVECTOR THERAPEUTICS	FRANCE	influenza vaccine
	BIOVECTOR THERAPEUTICS	FRANCE	interleukin-2 cancer vaccine
	BORAN PHARMACEUTICALS	SOUTH KOREA	Japanese encephalitis vaccine
	CELLGENIX TECHNOLOGIE TRANSFER	GERMANY	lymphoma vaccine
	CEL-SCI CORP. (VIRAL TECHNOLOGIES)	UNITED STATES	LEAPS-101
	CENTER OF MOLECULAR IMMUNOLOGY	CUBA	ganglioside vaccine
	CENTER OF MOLECULAR IMMUNOLOGY	CUBA	
	CHIRON	UNITED STATES	Neisseria meningococcus C vaccine
	CHIRON	UNITED STATES	rp24
	CHIRON (BIOCINE)	UNITED STATES	helicobacter pylori vaccine
	COLEY PHARMACEUTICAL GROUP	UNITED STATES	CpG 7909
	COLEY PHARMACEUTICAL GROUP	UNITED STATES	CpG DNA adjuvant
	CONNETICS CORP. (CONNECTIVE THERAPEUTICS)	UNITED STATES	rheumatoid arthritis vaccine
	CORIXA	UNITED STATES	tuberculosis vaccine
	CORIXA	UNITED STATES	Her-2/Neu peptides
	CORIXA	UNITED STATES	Muc-1 vaccine
	CORIXA	UNITED STATES	colon cancer vaccine
	CORIXA	UNITED STATES	leishmaniasis vaccine
	CORIXA	UNITED STATES	DTaP vaccine with MPL adjuvant
CORIXA (ANERGEN)	UNITED STATES		

CYTOVAX BIOTECHNOLOGIES	CANADA	pseudomonas vaccine
CYTRX (VAXCEL)	UNITED STATES	influenza vaccine
DENDREON CORP.	UNITED STATES	anti Her2-neu vaccine
DYNPORT VACCINE CO.	UNITED STATES	smallpox vaccine
ENICHIMICA (SCLAVO)	ITALY	bcr-abl peptide vaccine
GENZYME	UNITED STATES	melanoma gene based vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	h. pylori vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	hepatitis-B DNA vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	influenza vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	HIV vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	NefTat and gp120, with AS02
HENDERSON MORLEY	UNITED KINGDOM	CMV vaccine
IMCLONE SYSTEMS, INC.	UNITED STATES	gonorrhea vaccine
IMMUNE NETWORK	CANADA	Her-2 cancer vaccine
IMMUNE RESPONSE CORP.	UNITED STATES	brain cancer gene therapy
IMMUNE RESPONSE CORP.	UNITED STATES	MBGM-CSF VACCINE
IMMUNOMEDICS, INC.	UNITED STATES	anticancer vaccine
INTRACEL CORP.	UNITED STATES	ASI-BCL
IOMAI	UNITED STATES	ETEC vaccine
IOMAI	UNITED STATES	H pylori vaccine
IOMAI	UNITED STATES	cancer vaccine
JOHNSON & JOHNSON (CENTOCOR)	UNITED STATES	Genevax cancer vaccine
LARGE SCALE BIOLOGY CORP. (BIOSOURCE TECHNOLOGIES)	UNITED STATES	NHL vaccine
MEDIMMUNE	UNITED STATES	HPV-18 vaccine
MERCK & CO	UNITED STATES	AIDS vaccine
MERCK & CO	UNITED STATES	influenza vaccine
METACINE	UNITED STATES	dendritic cell cancer vaccine
MICROSCIENCE	UNITED KINGDOM	typhoid vaccine
NOVARX CORP	UNITED STATES	AUTOLOGOUS TUMOR CELLS/IL-2 MOD.FIBROBLASTS
OXFORD UNIVERSITY	UNITED KINGDOM	AIDS vaccine
OXXON PHARMACCINES	UNITED KINGDOM	melanoma vaccine
OXXON PHARMACCINES	UNITED KINGDOM	AIDS vaccine
OXXON PHARMACCINES	UNITED KINGDOM	hepatitis B vaccine
OXXON PHARMACCINES	UNITED KINGDOM	malaria vaccine
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	HBV DNA vaccine
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	HBV DNA vaccine
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	cancer DNA vaccine
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	cancer DNA vaccine
QLT	CANADA	PDV photodynamic vaccine
SHIRE	UNITED KINGDOM	
SHIRE	UNITED KINGDOM	haemophilus vaccine
SHIRE	UNITED KINGDOM	influenza vaccine
SHIRE (BIOCHEM PHARMA)	UNITED KINGDOM	influenza vaccine, nasal
SIGA TECHNOLOGIES, INC.	UNITED STATES	group A streptococcal vaccine
SIGA TECHNOLOGIES, INC.	UNITED STATES	bacterial commensal vector
SOLVAY	BELGIUM	influenza vaccine
THERION BIOLOGICS CORP.	UNITED STATES	trivalent HIV-1 IIIB vaccine
THERION BIOLOGICS CORP.	UNITED STATES	MUC-1 VACCINE
THERION BIOLOGICS CORP.	UNITED STATES	gene based NY-ESO-1 vaccine
THERION BIOLOGICS CORP.	UNITED STATES	CEA antigen
UNITED BIOMEDICAL	UNITED STATES	HIV-1 MN octameric vaccine
UNITED BIOMEDICAL	UNITED STATES	LHRH-base prostate cancer vaccine
WYETH	UNITED STATES	travelers' diarrhea vaccine
WYETH	UNITED STATES	RSV/PIV combination vaccine
WYETH (LEDERLE-PRAXIS)	UNITED STATES	herpes vaccine
WYETH (WYETH-AYERST)	UNITED STATES	
XENOVA	UNITED KINGDOM	DISC-GM-CSF
XENOVA	UNITED KINGDOM	TA-CIN
XENOVA (IMMULOGIC)	UNITED KINGDOM	TA-NIC
ZONAGEN	UNITED STATES	prostate cancer vaccine
ELAN	IRELAND	Alzheimers disease vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	acellular pertussis vaccine
ONCOLYTICS BIOTECH	CANADA	

Phase I / II	APHTON CORPORATION	UNITED STATES	anti-hCG vaccine
	AURX	UNITED STATES	HSV-2 vaccine
	AVAX TECHNOLOGIES, INC.	UNITED STATES	melanoma vaccine
	BIOQUEST	UNITED STATES	AIDS immunity vaccine
	BIOSTAR (STAR BIOTECH)	CANADA	GnRH immunotherapeutic
	GENZYME (GENZYME MOLECULAR ONCOLOGY)	UNITED STATES	
	ID BIOMEDICAL	CANADA	GAS vaccine
	IMMUNE RESPONSE CORP.	UNITED STATES	Vbeta6.2/6.5 T cell receptor
	JENNER BIOTHERAPIES	UNITED STATES	KSA ANTIGEN
	JOHNSON & JOHNSON (CENTOCOR)	UNITED STATES	ovarian cancer Mab
	MEDIGENE	GERMANY	HPV vaccine
	MEDIMMUNE	UNITED STATES	B19 parvovirus vaccine
	MERCK & CO	UNITED STATES	AIDS vaccine
	SR PHARMA	UNITED KINGDOM	Her-1 vaccine
	VIVENTIA BIOTECH (NOVOPHARM)	CANADA	4B5
	WYETH (WYETH-AYERST)	UNITED STATES	RSV vaccine
	Phase II	ACAMBIS	UNITED KINGDOM
ACAMBIS (ORAVAX)		UNITED KINGDOM	JE vaccine
ACAMBIS (ORAVAX)		UNITED KINGDOM	clostridium vaccine
ACAMBIS (PEPTIDE THERAPEUTICS)		UNITED KINGDOM	typhoid vaccine
ALTAREX CORP.		UNITED STATES	OREGOVOMAB
ANTEX BIOLOGICS		UNITED STATES	otitis media vaccines
ANTEX BIOLOGICS (MICROCARB)		UNITED STATES	helicobacter pylori vaccine
APHTON CORPORATION		UNITED STATES	anti-GnRH immunogen
AVANT IMMUNOTHERAPEUTICS INC.		UNITED STATES	cholera vaccine
AVANT IMMUNOTHERAPEUTICS INC.		UNITED STATES	cholera vaccine
AVANT IMMUNOTHERAPEUTICS INC.		UNITED STATES	typhoid vaccine
AVANT IMMUNOTHERAPEUTICS INC.		UNITED STATES	CETP vaccine
AVANT IMMUNOTHERAPEUTICS INC. (VIRUS RESEARCH INSTITUTE)		UNITED STATES	rotavirus vaccine
AVAX TECHNOLOGIES, INC.		UNITED STATES	breast cancer vaccine
AVAX TECHNOLOGIES, INC.		UNITED STATES	leukemia vaccine
AVAX TECHNOLOGIES, INC.		UNITED STATES	ovarian cancer vaccine
AVENTIS (AVENTIS PASTEUR)		FRANCE	ALVAC-HIV1
AVENTIS (AVENTIS PASTEUR)		FRANCE	ALVAC-HIV env, gag, pro
AVENTIS (AVENTIS PASTEUR)		FRANCE	AIDS vaccine
AVENTIS (AVENTIS PASTEUR)		FRANCE	cytomegalovirus vaccine, gene-based
AVENTIS (AVENTIS PASTEUR)		FRANCE	dengue vaccine
AVENTIS (AVENTIS PASTEUR)		FRANCE	HIB/HepB/IPV vaccine
AVENTIS (AVENTIS PASTEUR)		FRANCE	influenza vaccine, inj
AVENTIS (AVENTIS PASTEUR)		FRANCE	measles, mumps, and rubella virus vaccine
AVENTIS (AVENTIS PASTEUR)		FRANCE	meningococcal A/C/Y vaccine
AVENTIS (AVENTIS PASTEUR)		FRANCE	RSV vaccine
AVENTIS (AVENTIS PASTEUR)		FRANCE	streptococcus B vaccine
AVENTIS (AVENTIS PASTEUR)		FRANCE	streptococcus vaccine
AVENTIS (BEHRINGWERKE)		FRANCE	AIDS vaccine
AVENTIS (VIROGENETICS)		FRANCE	ALVAC-MN 120 TMG
AVENTIS (VIROGENETICS)		FRANCE	NYVAC-7
BARR LABORATORIES		UNITED STATES	JE vaccine
BAUSCH & LOMB		UNITED STATES	cytomegalovirus vaccine
BAUSCH & LOMB		UNITED STATES	CMV vaccine
BAVARIAN NORDIC RESEARCH INSTITUTE		DENMARK	MVA-BN AIDS vaccine
BAVARIAN NORDIC RESEARCH INSTITUTE		DENMARK	melanoma vaccine
BAXTER INTERNATIONAL (NORTH AMERICAN VACCINE)		UNITED STATES	streptococcus B vaccine,
BIOENVISION		UNITED KINGDOM	cancer vaccine
BIOMIRA INC.		CANADA	
BIOVECTOR THERAPEUTICS		FRANCE	
BIOVECTOR THERAPEUTICS		FRANCE	influenza vaccine
BRISTOL-MYERS SQUIBB		UNITED STATES	BMS-200475
CELL GENESYS INC. (SOMATIX)		UNITED STATES	GM-CSF gene modified cancer vaccine
CELL GENESYS INC. (SOMATIX)		UNITED STATES	
CEL-SCI CORP.		UNITED STATES	AIDS vaccine
CENTER OF MOLECULAR IMMUNOLOGY		CUBA	ganglioside vaccine
CHEIL JEDANG		SOUTH KOREA	Ps aeruginosa vaccine
CHIRON	UNITED STATES	vaccine HIV VCP-205/SF-2 rgp120	

CHIRON	UNITED STATES	hepatitis-B vaccine
CHIRON	UNITED STATES	DPT/Hib vaccine
CHIRON	UNITED STATES	meningococcal B vaccine
CHIRON	UNITED STATES	AIDS vaccine
CHIRON (BIOCINE)	UNITED STATES	HIV gp120 glycosylated +MF59
CIRCASSIA	UNITED KINGDOM	
COMMONWEALTH SERUM LABORATORIES	AUSTRALIA	influenza vaccine
COMMONWEALTH SERUM LABORATORIES	AUSTRALIA	HPV vaccine
CONNETICS CORP (CONNECTIVE THERAPEUTICS)	UNITED STATES	TCR receptor peptides
CORIXA	UNITED STATES	psoriasis vaccine
CORIXA	UNITED STATES	influenza vaccine with MPL adjuvant
CORIXA	UNITED STATES	malaria vaccine with MPL adjuvant
CORIXA (ANERGEN)	UNITED STATES	DR4/1-peptide
CORIXA (ANERGEN)	UNITED STATES	
CORIXA (ANERGEN)	UNITED STATES	AG4263
CRC TECHNOLOGY	UNITED KINGDOM	HPV vaccine
DENDREON CORP.	UNITED STATES	
DYNAVAX	UNITED STATES	hepatitis B vaccine
ENZO BIOCHEM	UNITED STATES	hepatitis-B therapy
GENELABS	UNITED STATES	hepatitis-E vaccine
GENZYME (GENZYME MOLECULAR ONCOLOGY)	UNITED STATES	DC-tumor fusion
GLAXOSMITHKLINE	UNITED KINGDOM	allergy vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	Epstein Barr virus vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	human papilloma virus vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	malaria vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	meningitis vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	RSV vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	
GLAXOSMITHKLINE (SB BIO)	UNITED KINGDOM	RTS,S/AS02
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	cancer vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	hepatitis A+B vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	lyme disease vaccine, three component
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	Neisseria meningitis A/C vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	streptococcus pneumoniae vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	typhoid vaccine
GLYCOGENESYS (SAFESCIENCE)	UNITED STATES	NCCG
HIV-VAC, INC.	CANADA	AIDS vaccine
ID BIOMEDICAL	CANADA	influenza vaccine
ID BIOMEDICAL	CANADA	Shigella flexneri vaccine
ID BIOMEDICAL	CANADA	Shigella sonnei vaccine
ID BIOMEDICAL (ID VACCINE)	CANADA	AIDS vaccine
IMMTECH INTERNATIONAL	UNITED STATES	rmCRP
IMMUNE RESPONSE CORP.	UNITED STATES	V9beta)3 and V(beta)13.1
IMMUNE RESPONSE CORP.	UNITED STATES	Vbeta14 T cell receptor
IMMUNE RESPONSE CORP.	UNITED STATES	Vbeta17 T cell receptor
IMMUNE RESPONSE CORP.	UNITED STATES	
IMMUNE RESPONSE CORP.	UNITED STATES	TCR vaccine
IMMUNO-DESIGNED MOLECULES	FRANCE	Dendritophages
INFLAMMATICS	UNITED STATES	
INNOGENETICS	BELGIUM	therpaeutic hepatitis-C vaccine
IOMAI	UNITED STATES	tetanus vaccine
JENNER BIOTHERAPIES	UNITED STATES	PSA vaccine
LUDWIG INSTITUTE FOR CANCER RESEARCH	BELGIUM	HPV vaccine
MEDIGENE	GERMANY	CVLP vaccine
MEDIMMUNE	UNITED STATES	UTI vaccine
MEDIMMUNE	UNITED STATES	HPV-11 vaccine
MEDIMMUNE	UNITED STATES	HPV-16 vaccine
MEDIMMUNE	UNITED STATES	MEDI 503 + MEDI 504
MEDIMMUNE	UNITED STATES	EBV vaccine
MEDIMMUNE	UNITED STATES	parainfluenza type 3 vaccine
MERCK & CO	UNITED STATES	AIDS vaccine
MERCK & CO	UNITED STATES	pneumococcal vaccine
MERCK & CO	UNITED STATES	streptococcus pneumoniae vaccine
MERCK KGAA	GERMANY	cancer vaccine

	NABI	UNITED STATES	Altastaph
	NEUROCRINE BIOSCIENCES	UNITED STATES	diabetes vaccine
	NEUROCRINE BIOSCIENCES	UNITED STATES	multiple sclerosis vaccine
	NORTHWEST BIOTHERAPEUTICS	UNITED STATES	
	NOVARTIS (BIOCINE)	SWITZERLAND	env2-3 gp120 vaccine
	NOVARX CORP	UNITED STATES	TGF-Beta antisense lung cancer vaccine
	NOVAVAX	UNITED STATES	HPV-16 VLP vaccine
	NOVAVAX	UNITED STATES	hepatitis-E vaccine
	ONYVAX LTD.	UNITED KINGDOM	anti-gp72 MAbs
	ONYVAX LTD.	UNITED KINGDOM	
	ONYVAX LTD.	UNITED KINGDOM	
	OXFORD BIOMEDICA	UNITED KINGDOM	
	PEPTOR	ISRAEL	DiaPep277
	PHARMEXA	DENMARK	TNF-alpha vaccine
	PROGENICS PHARMACEUTICALS	UNITED STATES	MGV
	PROTEIN SCIENCES	UNITED STATES	cancer vaccine
	PROTHERICS	UNITED KINGDOM	GnRH immunotherapeutic
	PROTHERICS	UNITED KINGDOM	angiotensin vaccine
	SR PHARMA	UNITED KINGDOM	SRP299
	THERION BIOLOGICS CORP.	UNITED STATES	ALVAC-CEA/B7.1
	THERION BIOLOGICS CORP.	UNITED STATES	rv-gp100
	THERION BIOLOGICS CORP.	UNITED STATES	ALVAC Mage1, Mage 3, gp100
	THERION BIOLOGICS CORP.	UNITED STATES	tyrosinase melanoma vaccine
	THERION BIOLOGICS CORP.	UNITED STATES	VACCINIA, PSA ANTIGEN
	TITAN PHARMACEUTICALS (TRILEX)	UNITED STATES	
	TITAN PHARMACEUTICALS (TRILEX)	UNITED STATES	
	TRANSGENE	FRANCE	MVA-Muc1-IL2
	TRANSGENE	FRANCE	cervical cancer vaccine
	VAXGEN	UNITED STATES	monovalent gp120 vaccine
	VECTOR MEDICAL TECHNOLOGIES	UNITED STATES	met-enkephalin vaccine
	VICAL	UNITED STATES	malaria vaccine
	VICAL	UNITED STATES	RSV vaccine, gene-based
	VICAL	UNITED STATES	
	VICAL	UNITED STATES	gp100 vaccine
	VICAL	UNITED STATES	IL-2 gene therapy
	VIRAX	AUSTRALIA	AIDS vaccine
	VIROPHARMA	UNITED STATES	VP-50406
	WEST PHARMACEUTICAL SERVICES, INC.	UNITED STATES	ChiSys-influenza vaccine
	WYETH (APOLLON)	UNITED STATES	gp160 gene vaccine
	WYETH (APOLLON)	UNITED STATES	hepatitis-B vaccine, gene-based
	WYETH (LEDERLE-PRAXIS)	UNITED STATES	RSV subunit vaccine
	WYETH (LEDERLE-PRAXIS)	UNITED STATES	parainfluenza virus vaccine
	WYETH (WYETH-AYERST)	UNITED STATES	hepatitis C vaccine
	WYETH (WYETH-AYERST)	UNITED STATES	influenza vaccine bivalent type A
	XENOVA (CANTAB)	UNITED KINGDOM	DISC-PRO vaccine
	XENOVA (CANTAB)	UNITED KINGDOM	TA-HPV
	XENOVA (IMMULOGIC PHARMACEUTICAL)	UNITED KINGDOM	
	YM BIOSCIENCES	CANADA	cancer vaccine
	NEUROCRINE BIOSCIENCES	UNITED STATES	multiple sclerosis vaccine
	PHARMEXA (M&E BIOTECH)	DENMARK	HER-2 DNA vaccine
Phase II / III	ANTEX BIOLOGICS (MICROCARB)	UNITED STATES	campylobacter vaccine
	ANTIGENICS, INC. (AQUILA BIOPHARMACEUTICALS)	UNITED STATES	pneumococcal conjugate vaccine
	DIAMYD MEDICAL	SWEDEN	
Phase III	IMMUNIZATION PRODUCTS	UNITED STATES	Salk HIV Immunogen
	ACAMBIS (ORAVAX)	UNITED KINGDOM	H. pylori vaccine
	ACAMBIS (PEPTIDE THERAPEUTICS)	UNITED KINGDOM	vaccine, yellow fever
	ACTIVE BIOTECH	SWEDEN	EPEC vaccine, SBL
	ANTIGENICS, INC.	UNITED STATES	HSPPC-96
	ANTIGENICS, INC.	UNITED STATES	QS-21
	ANTIGENICS, INC. (AQUILA BIOPHARMACEUTICALS)	UNITED STATES	malaria vaccine SPf66
	ANTISOMA	UNITED KINGDOM	pentumomab
	APHTON CORPORATION	UNITED STATES	antigastrin-17 immunogen
	AVENTIS (AVENTIS PASTEUR)	FRANCE	diphtheria & tetanus toxoids & hepatitis B antigen vaccine
	AVENTIS (AVENTIS PASTEUR)	FRANCE	DTPa vaccine

AVENTIS (AVENTIS PASTEUR)	FRANCE	haemophilus-DTP vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	acellular pertussis DTP
AVENTIS (AVENTIS PASTEUR)	FRANCE	acellular pertussis vaccine
AVENTIS (AVENTIS PASTEUR)	FRANCE	rabies vaccine
AVENTIS (CONNAUGHT)	FRANCE	rabies vaccine
AVENTIS (PASTEUR MERIEUX MSD)	FRANCE	hepatitis-A vaccine
AVI BIOPHARMA INC.	UNITED STATES	hCG CTP-37 peptide
BAXTER INTERNATIONAL (AMVAX)	UNITED STATES	aP vaccine
BAXTER INTERNATIONAL (IMMUNO AG)	UNITED STATES	tick-borne encephalitis vaccine, inactivated
BAXTER INTERNATIONAL (NORTH AMERICAN VACCINE)	UNITED STATES	DTaP-IPV-Hib vaccine
BAXTER INTERNATIONAL (NORTH AMERICAN VACCINE)	UNITED STATES	DTaP-IPV vaccine
BERNA SA	SWITZERLAND	
BERNA SA (SWISS SERUM AND VACCINE INSTITUTE)	SWITZERLAND	rabies vaccine
BIOMERIEUX-PIERRE FABRE (FABRE)	FRANCE	BBG2Na
BIOMIRA INC.	CANADA	adenocarcinoma vaccine
BIOTA	AUSTRALIA	
BIO-TECHNOLOGY GENERAL	UNITED STATES	hepatitis-B vaccine
BIOVEST	UNITED STATES	idiotype tumor vaccine
BTG	UNITED STATES	hepatitis-B vaccine
CANCERVAX CORP.	UNITED STATES	cancer vaccine
CELLTECH	UNITED KINGDOM	tetanus and diphtheria vaccine
CELLTECH	UNITED KINGDOM	vaccine, yellow fever
CENTER OF MOLECULAR IMMUNOLOGY	CUBA	meningitis vaccine
CHIRON	UNITED STATES	pertussis vaccine
CHIRON (BEHRINGWERKE)	UNITED STATES	TBE vaccine
CHIRON (BIOCINE)	UNITED STATES	meningococcus C vaccine
CHIRON (BIOCINE)	UNITED STATES	meningococcus A & C vaccine
CHIRON (BIOCINE)	UNITED STATES	hepatitis-A vaccine
CHIRON (BIOCINE)	UNITED STATES	acellular pertussis vaccine
CHIRON (BIOCINE)	UNITED STATES	adjuvanted influenza vaccine
COMMONWEALTH SERUM LABORATORIES	AUSTRALIA	
CORIXA	UNITED STATES	allergy vaccine
CORIXA	UNITED STATES	hepatitis-B vaccine with MPL adjuvant
CORIXA	UNITED STATES	herpes virus vaccine
CORIXA (RIBI IMMUNOCHEM)	UNITED STATES	melanoma vaccine
DAIICHI PHARMACEUTICAL	JAPAN	DF-098
DENDREON CORP.	UNITED STATES	
DYNAVAX	UNITED STATES	Amb a 1 immunostim conjugate
GENITOPE	UNITED STATES	lymphoma vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	chlamydia vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	
GLAXOSMITHKLINE	UNITED KINGDOM	E coli vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	hepatitis-A + salmonella vaccine
GLAXOSMITHKLINE	UNITED KINGDOM	herpes simplex vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	diphtheria, tetanus, acellular pertussis, hepatitis-B, inactivated polio, haemophilus b vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	diphtheria, tetanus, acellular pertussis, hepatitis-B, haemophilus b vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	diphtheria and tetanus toxoids acellular pertussis hepatitis B recombinant inactivated polio virus vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	haemophilus influenzae type b vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	hepatitis-A/typhoid vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	hepatitis-B vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	hepatitis-B vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	MMR vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	MMR/varicella vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	strep. Pneumoniae vaccine
GLAXOSMITHKLINE (SMITHKLINE BEECHAM BIOLOGICALS)	UNITED KINGDOM	varicella vaccine
HENDERSON MORLEY	UNITED KINGDOM	herpes simplex vaccine
IMCLONE SYSTEMS, INC.	UNITED STATES	mitunomab
IMMUNE RESPONSE CORP.	UNITED STATES	HIV therapy
IMMUNE RESPONSE CORP.	UNITED STATES	Combinationn arthritis vaccine
INTRACEL CORP. (PERIMMUNE)	UNITED STATES	cancer vaccine
MACROPHARM	GERMANY	cancer vaccine

MEDIMMUNE	UNITED STATES	influenza vaccine, trivalent, types A + B live, cold adapted
MERCK & CO	UNITED STATES	herpes zoster vaccine
MERCK & CO	UNITED STATES	human papilloma virus vaccine
MERCK & CO	UNITED STATES	
MERCK & CO	UNITED STATES	rotavirus vaccine
NABI (UNIVAX BIOLOGICS)	UNITED STATES	staphylococcus aureus vaccine
NATIONAL INSTITUTE OF PUBLIC HEALTH	NORWAY	meningococcus B vaccine
NORTHWEST BIOTHERAPEUTICS	UNITED STATES	prostate cancer vaccine
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	malaria vaccine
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	ETEC vaccine
POWDERJECT PHARMACEUTICALS	UNITED KINGDOM	
POWDERJECT PHARMACEUTICALS (EVANS VACCINES)	UNITED KINGDOM	hepatitis-B vaccine
PROGENICS PHARMACEUTICALS	UNITED STATES	GMK
PROVALIS	UNITED KINGDOM	pseudomonas vaccine
RHEIN BIOTECH	NETHERLANDS	hepatitis B vaccine
RHEIN BIOTECH	NETHERLANDS	typhoid vaccine
SHIRE	UNITED KINGDOM	influenza vaccine
STRESSGEN BIOTECHNOLOGIES CORP.	CANADA	HSP65 FUSION W/E7 PROTEIN
TAIHO	JAPAN	tazobactam + piperacillin
TITAN PHARMACEUTICALS	UNITED STATES	
VAXGEN	UNITED STATES	bivalent gp120 vaccine Vaxgen B3
VAXGEN	UNITED STATES	HIV vaccine
VICAL	UNITED STATES	HLA-B7 gene therapy
WYETH	UNITED STATES	9-valent pneumococcal conjugate vaccine
WYETH	UNITED STATES	9-valent pneumococcal conjugate - meningococcal Group C conjugate vaccine
WYETH (LEDERLE-PRAXIS)	UNITED STATES	meningococcal vaccine

Source: Tufts Center for the Study of Drug Development, Tufts University, 2002