

## The Vaccine Industry: Does It Need a Shot in the Arm?

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**Overview** — *This paper broadly examines the scientific, regulatory, and economic factors that contribute to constrained vaccine production capacity, periodic vaccine shortages, and perceptions of inadequate investment in new vaccine product development. It describes the vaccine development and production processes and summarizes how regulatory requirements influence these activities. Market dynamics related to vaccine supply and demand are also explored, including an examination of the industry's cost structure, potential market size, and purchaser price sensitivity. A broad range of policy interventions designed to address shortcomings of the vaccine market are considered.*

## Contents

THE VACCINE PRODUCT .....	3
Research and Development .....	4
Table 1: Number of Licensed Vaccine Products for Viruses and Toxins, 2005 .....	5
Product Equals Process .....	8
Vaccine Production .....	10
THE VACCINE MARKET .....	12
Winner(s) Take All .....	13
Bigger Fish to Fry .....	17
Liability: The Straw That Broke the Camel’s Back .....	20
POLICY INTERVENTIONS .....	21
Push Proposals .....	21
Pull Proposals .....	25
CONCLUSION .....	32
ENDNOTES .....	32

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# The Vaccine Industry: Does It Need a Shot in the Arm?

Vaccines were among the first “wonder drugs” to radically transform human health and longevity. In doing so, they also permanently altered public expectations of medical science.

Infectious diseases were once the greatest threat to public health and the leading cause of death. Advances in vaccine development, combined with improved sanitation and antibiotics, have greatly reduced the threat of infectious disease such that most Americans are unaware of lingering dangers.

The American public has come to expect that vaccines will be available to protect them against most infectious diseases and that policy interventions will be pursued if that availability is compromised. Vaccines are unique among pharmaceutical products—they prevent, rather than treat, disease; they protect communities, as well as individuals. The preventive and collective benefits of vaccines create a powerful public interest in ensuring the availability of these products. Despite their promises of protection from disease, vaccines have provoked controversy and troubled policymakers since the first vaccination in 1796.

Recent headlines underscore the current concerns related to vaccines: shortages of childhood vaccines, long lines at flu shot clinics, skepticism regarding vaccine safety, and fears related to bioterror and avian flu threats. All illustrate the negative way vaccines are viewed by the public. These headlines also suggest there are problems in the vaccine market that threaten to undermine availability of existing vaccines and hinder the development of new products that could offer superior, more extensive disease protection.

## THE VACCINE PRODUCT

Traditional vaccines are substances developed in a laboratory setting that stimulate the body’s immune system to prevent or control an infection by a bacterial or viral agent. (Therapeutic vaccines serve a different purpose; see sidebar, page 6.) Vaccines are typically made from “attenuated” live microorganisms (or “microbes”); inactivated, whole microorganisms; isolated components of a microbe; or materials, such as toxins, produced by a disease-causing agent. Vaccine products can be administered orally; injected into the skin, muscle, or bloodstream; or inhaled as an aerosol.

Vaccines are highly specific to the particular disease agent from which they are derived. In some ways, they mimic the disease-causing agent in order

to stimulate the immune system to produce antibodies against it. Ideally, once the body “learns” to create the antibody to ward off a specific disease, it retains the memory of the antigen presented by the vaccine and will produce antibodies in response to the antigen if exposed to it again. In this way, vaccines are meant to “teach” the body how to fight off the targeted disease-causing agent.

Currently the Food and Drug Administration (FDA) has licensed 51 vaccine products for use in the United States, offering protection against 21 infectious diseases, as shown in Table 1 (next page). Some of these products are combination vaccines that protect against multiple diseases. Vaccines have also been developed for some infectious disease threats beyond those identified in Table 1. However, these vaccines are not available in the U.S. market either because they were withdrawn from the market (such as the cholera vaccine) or because market approval from the FDA for these products has not yet been sought or granted (such as the tick-borne encephalitis vaccine<sup>1</sup>).

The effectiveness of different vaccines targeting the same disease-causing agent can vary depending on how each vaccine is made and administered. In general, “live” vaccines provide a more potent immune response but may also pose greater safety risks relative to inactivated or “killed” vaccines. Some vaccines are suitable for adult populations but are inappropriate for, or untested in, pediatric populations.

## Research and Development

Like all pharmaceutical products, vaccine products require market approval from the FDA before they can be sold. To secure such approval, manufacturers must conduct laboratory and clinical research to prove the safety and efficacy of their products. This product-focused research and development is predicated on basic research that explores the physiological and genetic makeup of microorganisms, the human immune response, and the ways in which microbes interact with human host cells, often using animal models.

This type of basic research triggers “vaccine discovery” efforts to identify and test potential antigens that could be targets for a vaccine-induced immune response. Such research also aids the development of techniques

### Common Vaccine-Related Terms

**Adjuvant** – A substance, such as salt or oil, that increases the immune response to a given antigen.

**Antibody** – A substance produced by the body in response to the presence of a specific antigen. The body uses antibodies to bind antigens and to prevent and fight disease.

**Antigen** – A substance that triggers an immune response. Antigens derived from a microorganism’s outer surface, such as proteins, are typically most effective in prompting an immune response that prevents infection and protects against disease.

**Attenuation** – The process of reducing the virulence of a microorganism, often as a result of continued growth in an artificial host or culture system.

**Conjugate Vaccine** – Created by attaching a weak antigen, such as a polysaccharide, to a protein to elicit a stronger, longer-lasting immune response. Young children do not respond to polysaccharide vaccines; conjugates are sometimes used to confer immunity for this population.

**Stabilizers** – Materials that protect the vaccine from environmental factors, such as temperature, light, and humidity which could erode the vaccine’s effectiveness.

**Toxoid** – A toxin rendered harmless, but still capable of acting as an antigen.

**TABLE 1**  
**Number of Licensed Vaccine Products for Viruses and Toxins, 2005**

<b>Disease (Vaccine Target)</b>	<b>Licensed Vaccine Products (Uses)</b>	<b>Manufacturers</b>
<b>Anthrax</b> ( <i>B. Anthracis</i> )	1	1
<b>Diphtheria</b> ( <i>C. diphtheriae</i> toxin)	11* (5 adult*/booster, 6 pediatric)	4
<b>Hepatitis A Virus</b>	3	2
<b>Hepatitis B Virus</b>	5	2
<b>Influenza A and B</b>	4 (4 adult, 2 pediatric)	4
<b>Japanese Encephalitis Virus</b>	1	1
<b>Measles (Rubeola) Virus</b>	4	1
<b>Meningitis</b> ( <i>H. influenzae b</i> or HIB)	4	3
<b>Meningococcal disease</b> ( <i>N. meningitides</i> )	2	1
<b>Mumps Virus</b>	4	1
<b>Pneumonia</b> ( <i>S. pneumoniae</i> )	2 (1 adult, 1 pediatric)	2
<b>Polio Virus</b>	3*	2
<b>Rabies Virus</b>	3*	3
<b>Rubella Virus</b>	3	1
<b>Smallpox Virus</b>	1	1
<b>Tetanus</b> ( <i>C. tetani</i> toxin)	14*	3
<b>Tuberculosis</b> ( <i>M. tuberculosis</i> , <i>M. bovis</i> or BCG)	2	2
<b>Typhoid Fever</b> ( <i>S. typhi</i> )	2	2
<b>Chicken Pox/Varicella Virus</b>	2	2
<b>Yellow Fever Virus</b>	1	1
<b>Whooping Cough or Pertussis</b> ( <i>B. pertussis</i> )	4	3

\*One product not currently marketed.

Source: Center for Biologics Evaluation and Research, "Vaccines Licensed for Immunization and Distribution in the US," Food and Drug Administration, updated September 9, 2005; available at [www.fda.gov/cber/vaccine/licvacc.htm](http://www.fda.gov/cber/vaccine/licvacc.htm)

for producing and isolating these antigenic agents and for assessing the immune protection offered by vaccine candidates. Basic and vaccine discovery research is generally conducted by universities, small biotechnology companies, and some large pharmaceutical companies. Through the National Institutes of Health (NIH), the Department of Defense (DoD), and the Centers for Disease Control and Prevention (CDC), the federal government plays a major role in funding and, in some instances, directly conducting research related to vaccine discovery.<sup>2</sup>

If a vaccine candidate emerges from the discovery research, clinical trials in human subjects are used to test the safety and effectiveness of the potential vaccine. The four phases of this research, which mirror the structure of pre-market clinical research for chemically based pharmaceutical compounds, are described here.

**Phase I** — Phase I trials are typically limited to a small number of participants (20 to 80) and are frequently begun in adults and then include children if they are likely to be vaccinated with the candidate product.<sup>3</sup> These trials seek to gather preliminary data on the safety of the vaccine and its ability to trigger an immune response. Vaccine candidates that elicit an immune response are said to be immunogenic. Phase I trials are considered part of the discovery phase and, if the results of these limited trials are promising, vaccine development will begin.

**Phase II** — Phase II trials involve a larger number of participants (often several hundred). Phase II trials can be divided into two broad categories. Phase IIa studies seek to validate the preliminary data on safety and immunogenicity generated in Phase I trials. Phase IIb studies can be used to obtain more precise data on the magnitude of immune response as it relates to dosage and dose intervals, and they can also be focused on the populations for whom the vaccine is likely to be recommended. Although the data generated through IIb trials can sometimes provide a good sense of the vaccine candidate's efficacy, these estimates are too imprecise to be used for securing licensure. Candidate vaccines found to be safe and immunogenic will require additional study before market approval is granted.

**Phase III** — Phase III trials are large, randomized, double-blind, placebo-controlled studies that may enroll tens of thousands of participants.<sup>4</sup> These studies validate the safety and immunogenicity data generated through Phases I and II in a much larger and more diverse segment

### Therapeutic Vaccines

**Advances in immunology have led to the development of "therapeutic vaccines."** Therapeutic vaccines differ dramatically from the traditional vaccines in two ways: (i) they are intended to treat an existing disease rather than provide preventive protection and (ii) many of the therapeutic vaccine approaches are specifically formulated for individual patients, often relying on clinical specimens from the patient, such as white blood cells, to create the vaccine. Although these vaccines stimulate an immune response they do not have broad, population-wide application.

Therapeutic vaccines for cancer are being investigated as ways to increase the body's natural defense response to cancer antigens. The vaccines are being developed based on increased understanding of how the immune system responds and why certain cancerous cells are not identified by the immune system until tumors have begun to develop.

of the overall population. Phase III studies also measure vaccine efficacy and safety among vaccine recipients relative to a control group, usually placebo recipients.

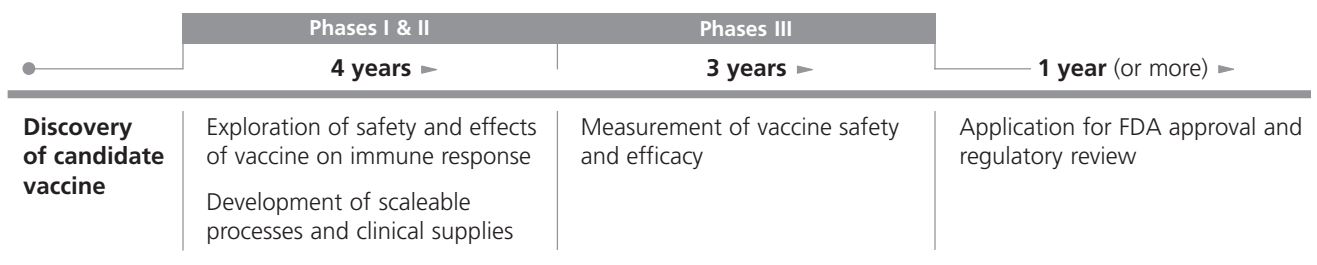
Phase III studies generally seek to demonstrate that the actual incidence of disease in vaccine recipients is significantly lower than the disease incidence in placebo recipients. Determining whether the immune response triggered by the vaccine actually confers disease protection requires long-term observation of study participants, often for two to three years. Because ethical considerations preclude an immediate, direct disease challenge (meaning, direct intentional exposure to the disease-causing agent), study participants must be monitored over time to see if they are protected from the disease-causing agent. The number of participants in such trials often needs to be very large, especially for vaccines directed against disease agents that are relatively uncommon.

Phase III trials also seek to prove a relationship between disease protection and the presence of immune response markers, such as antibody levels. Establishing such relationships allows subsequent studies of sub-populations to focus on these biomarkers, avoiding the protracted time frame required to observe disease incidence. Similarly, Phase III trials of vaccines directed at disease agents that are not naturally prevalent (such as those from bioterror threats) will be limited to measuring an immunological response, such as serum antibody level. These response markers can be correlated to actual disease protection, as demonstrated in animal models.

The costs of product development, particularly Phase III trials, are generally thought to be higher for vaccines than for pharmaceuticals. Because vaccines are given to healthy people, regulatory tolerance for health risks associated with these products tends to be extremely low. Vaccine trials are typically much larger than those conducted for pharmaceutical products because of this risk-averse orientation, as well as the need to test the product through a trial that appropriately represents the broad population intended for vaccination.

### Development of Vaccine for Human Papilloma Virus

Eight years have passed since Merck's discovery of a candidate vaccine for HPV. The pharmaceutical company is still awaiting final approval for market use.



Regulatory tolerance of risk tends to be balanced against the perceived benefits of the pharmaceutical product. Because vaccine products are given to healthy persons, the vaccine's benefits are a function of both the prevalence of the disease targeted and the extent to which the vaccine decreases the morbidity and mortality risks of that disease. In some cases, rare adverse events associated with a similar, previously marketed product can lead regulators to require very large trials to guard against safety risks. For example, some believe that very large trial size requirements were imposed on the recent trial of Aventis Pasteur's rotavirus vaccine due to infrequent but severe adverse events associated with a Wyeth rotavirus product that was ultimately pulled from the market.

**Phase IV** — FDA frequently asks for sizeable post-marketing studies to examine ancillary questions such as the effect of use on extended populations (that is, beyond the group for which the vaccine is initially intended) or for potential side effects with other medications already in use. These large follow-up studies have become almost a standard feature in the vaccine field, adding to the total cost for getting a new product established in the market. Though such studies answer important safety questions, they are perceived by some as commanding clinical trial resources that might otherwise be devoted to the development of more new vaccines.

Although government plays an important role in vaccine discovery and occasionally sponsors vaccine development work, the vaccine industry is primarily responsible for moving a vaccine beyond the "proof of concept" stage to a marketable product. Industry generally funds clinical trials in Phases II, III, and IV, although much of this industry-sponsored research may be conducted by universities and academic medical centers through research contracts. The industry is also the dominant sponsor for product development-related research. These types of research efforts focus on taking biological materials identified and produced in a small laboratory setting and turning these materials into products that can be manufactured on an industrial scale. Much of this research is conducted directly by large pharmaceutical companies. In 2000, the leading vaccine manufacturers spent approximately \$750 million on all research and development efforts, representing about 15 to 20 percent of vaccine revenues.<sup>5</sup>

## Product Equals Process

In many ways the vaccine "product" is actually the process used to create the vaccine. Legal recognition of vaccine products (found in both regulatory frameworks and intellectual property rights) are highly dependent on adherence to a defined production process, as opposed to chemical identification of the vaccine itself, because of the difficulties inherent in characterizing a product derived from a biological entity.

Unlike drug products, vaccines cannot be chemically analyzed to determine identity or composition, and potency or dosage is not a simple function of molecular weight. The precise nature of these biological products



in general has not been not fully defined, and the molecular properties that confer immune protection are not wholly understood. Furthermore, because vaccine products are based on living, adaptive organisms, small variations in the production process could potentially alter the organism, and therefore the vaccine, in unknowable ways. These alterations could have a profound impact on the product's safety or effectiveness.<sup>6</sup>

**Regulatory requirements** — Because the end product of vaccine production cannot be measured with precision, the FDA's regulatory oversight of vaccines focuses on the production process. Regulators demand strict compliance with well-defined production processes that are designed and validated by the manufacturer and approved by FDA. "Generic" biologics do not exist, because a new product cannot be established as biologically equivalent to a previously approved product given existing technology. This "bioequivalence" is something easily established in many other chemically based pharmaceutical products. Currently, every manufacturer must conduct extensive clinical trials to demonstrate that the product generated by their production process is safe and effective.

To assure the reliability of clinical trial results, FDA requires that the product used in Phase III trials are representative of those that will be marketed. Industry has generally found that this requirement necessitates that the vaccine used in the final stage of Phase II clinical testing be manufactured in the facility and with the processes intended for production of the eventual commercial product.

The FDA requires two separate approvals for the introduction of a biologic: an Establishment License Application (ELA), assuring the facility and process for manufacturing, and a Product License Application (PLA), containing data on the safety and efficacy of the product. In contrast, FDA drug approvals require only one approved application, the New Drug Application (NDA). Minor modifications in production process of vaccines, such as new packaging materials, may require regulatory approval and re-licensing of the production facility. In order to avoid unnecessary costs down the road, manufacturers generally build their commercial production facilities and seek their ELA before moving on to Phase III trials.

Even after a product has been FDA-approved, extensive quality control measures are also required to ensure ongoing compliance with specified production processes and to assure product integrity. In addition to this self-monitoring, manufacturers must submit samples of each vaccine lot to the FDA for approval before the lot can be sold. FDA inspectors will also periodically visit production facilities to verify adherence to regulatory guidelines established by current Good Manufacturing Practices.

Many of these process-bound regulatory approaches have the potential to change in the future as new technologies and techniques allow for improved analytic characterization of biologics. Some smaller biological molecules can already be defined and their structure and composition

can be accurately verified. In light of these advances, the European Union has cleared the way for generic versions of some biologic products. However, the advent of “end product”-oriented regulation of vaccines is not likely in the immediate future, as vaccines are very large and complex molecules that are particularly challenging to characterize.

**Patent protections** — Intellectual property rights related to vaccine products, as conferred through patent protections, typically hinge on technological breakthroughs in the production process, not on the vaccine product itself. Patents are generally not bestowed on materials found in nature, fundamentally limiting the patentability of a biological product like vaccines. To the extent vaccine products enjoy patent protection, they usually incorporate chemical additives, such as adjuvants or stabilizers, or are produced with novel techniques, such as genetic engineering.

Even when vaccine patents exist, conventional wisdom holds that patents for vaccines generally provide less commercial protection and value for producers than patents for chemical pharmaceuticals. Vaccine patents do not prohibit the sale of competing products created through alternative production processes. By engineering processes similar but not identical to the protected technology, competitors are able to bring comparable vaccines to market.<sup>7</sup> The substantial involvement by government agencies in early vaccine research also has raised questions about the value of patent positions, as these agencies tend to prefer nonexclusive licenses to patentable discoveries.

The complexities of vaccine production, coupled with the challenges of maintaining a scale suitable for producing tens of millions of doses, require both specialized facilities and highly trained personnel. Only a handful of organizations have the capital and expertise to meet these requirements. Consequently, only a small number of companies produce vaccine for the U.S. market. Although 11 manufacturers now hold vaccine product licenses, most vaccines are produced by four large pharmaceutical companies: Sanofi Aventis (formerly Aventis Pasteur), GlaxoSmithKline, Merck, and Wyeth.

## Vaccine Production

The production processes for manufacturing vaccines are highly complex, specialized, and time consuming. While the precise production methods can differ substantially among vaccines, some generalizations can be made. All vaccine production involves the growth and harvesting of microorganisms, either the disease-causing organism or another microorganism that has been modified or genetically engineered to produce the antigenic characteristics of the disease-causing agent.

**Cultivation** — Pathogenic organisms that grow remarkably well within the human body can prove difficult to culture under industrial manufacturing conditions. Microbial growth can be highly sensitive to

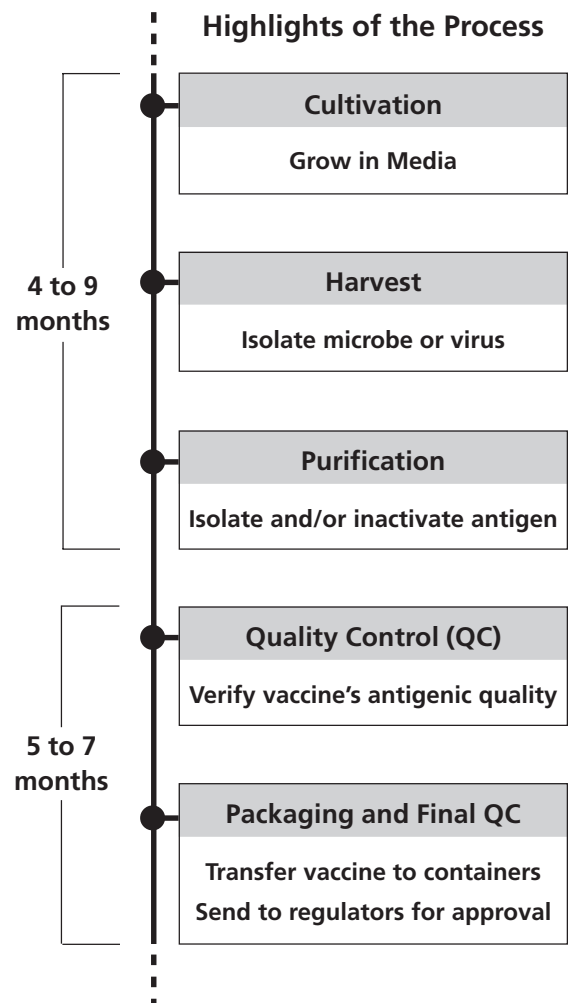
variations in temperature and to particular types of growth media. For example, viruses can only be grown in living cells, such as cell cultures and fertilized hen’s eggs. Small changes in environmental conditions or in the strain of microorganism used in the production process can significantly reduce the yield of biological material available to create the vaccine product. To further complicate matters, the very conditions that encourage growth of the target microorganism can often promote growth of unwanted contaminants, creating the need for powerful air filtration systems and the use of rigorous sterile techniques.

**Purification** — After the growth phase, additional steps are taken to isolate and, in some cases, inactivate the microorganism being used in vaccine preparation. In other cases, the microorganism is split into component parts and specific molecules with the appropriate antigenic qualities are isolated to serve as the basis of the vaccine. The active component of the vaccine is then isolated and blended with other materials to produce what is known as the bulk. It can take anywhere from four to nine months to cultivate the microbe and produce the bulk.

**Quality control** — Because small deviations in process can have a major impact on the potency and effectiveness of the vaccine product, stringent quality control procedures are used to verify that the vaccine product contains the desired antigenic material in the correct dosage and is free of contaminants. Quality control specialists employed by the manufacturer measure progress at each step of the production process through analysis of a variety of biomarkers, including protein content, viral infectivity, bacterial contamination, and endotoxin content.<sup>8</sup> Each batch must be tested against strict standards. Despite rigid compliance with standardized production protocols, assumptions regarding process integrity and product quality do not carry over from one batch to another. It can take up to three months to complete all necessary quality control activities.

**Packaging** — Following these quality control steps, the bulk is prepared for packaging. This process can involve freeze drying the product to extend its shelf life. The finished product is packaged in appropriate containers for delivery. Additional quality control tests are performed at this stage to ensure that the packaging process has not altered the safety or potency of the vaccine product and samples from each batch are sent to regulators for additional testing. Finishing the product from the bulk, including time for regulatory assessment, can take five to seven months, resulting in a total production time of 9 to 16 months.

**Vaccine Manufacture** – Manufacture of vaccine takes 9 to 16 months. Throughout the process, quality control measures are implemented.



## THE VACCINE MARKET

Vaccines are a small piece of the global pharmaceutical market, representing approximately 1.5 percent of all pharmaceutical revenues.<sup>9</sup> Worldwide sales of vaccines are estimated to be between \$4.8 and \$6 billion per year, with about a quarter of total sales in the United States (\$1.5 billion).<sup>10</sup> Pediatric vaccines make up the majority of the U.S. market, accounting for approximately 70 percent of domestic vaccine sales (see illustration, below).

Although it is small, the vaccine market continues to grow at a modest but steady rate. The global market for vaccines has grown about 10 percent per year since 1992 due largely to the worldwide effort to eradicate polio as well as the introduction of new, higher priced pediatric vaccine products in industrialized countries. For example, the recent introduction of a childhood pneumococcal vaccine effectively doubled the U.S. market due to its relatively high price and high uptake rate.

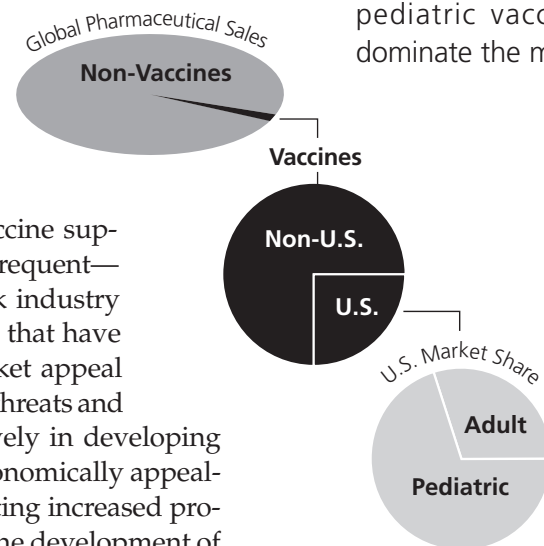
Other vaccine products introduced in the last decade represented improvements to existing vaccines rather than novel disease protection. These new, higher priced vaccines tended to displace existing products, resulting in less significant increases in overall sales. For example, when the safer, inactivated poliovirus vaccine was introduced, it rapidly replaced active oral poliovirus vaccine in clinical practice. The older vaccine was ultimately withdrawn from the market.

Market analysts anticipate strong vaccine market growth in the future. One information service that tracks commercial developments in the vaccine pipeline listed nearly 200 projects in the Phase II and Phase III stages of clinical trials in mid-2004.<sup>11</sup> Nearly 30 new vaccines are expected to be developed and marketed by 2010, including those offering protection against human papilloma virus (HPV) and human immunodeficiency virus (HIV), as well as therapeutic vaccines for melanoma and rheumatoid arthritis.

Despite historic and projected growth in the overall vaccine market, policymakers are deeply concerned about the perceived fragility of the nation's vaccine supply. These concerns are driven by sporadic—yet not infrequent—supply shortages for existing vaccines, as well as weak industry interest in the development and production of vaccines that have limited commercial appeal. Vaccines with limited market appeal include products directed against potential bioterrorism threats and those directed at diseases prevalent mostly or exclusively in developing countries. While some new vaccine products may be economically appealing to manufacturers, market forces are neither stimulating increased production capacity for existing vaccines nor encouraging the development of vaccines for diseases not currently prevalent in industrialized countries.

### Worldwide Pharmaceutical Sales and the U.S. Share of the Vaccine Market

Vaccines represent a very small portion of global pharmaceutical sales. About one quarter of vaccines are sold in the United States, where pediatric vaccine sales dominate the market.



## Winner(s) Take All

Prevailing market conditions have led to industry consolidations and product withdrawals, resulting in an overall decrease in the number of manufacturers engaged in vaccine production as well as a narrowing of the competitive field for specific product classes (vaccines that target the same disease agent). Many vaccines are now produced by only one manufacturer. Some analysts have concluded that the economic dynamics of the vaccine market preordain a small number of suppliers for any given product class. Although this “winner take all” dynamic does not guarantee a single, monopolistic supplier, there appears to be a general tendency for vaccine markets to drift toward one or few producers for a given product class because of the cost structure of vaccine production coupled with relatively low levels of demand for vaccine products.

**Limited market size** — Unlike drug or other commercial products, a person will use a vaccine product only a limited number of times in his or her lifetime. Therefore the potential market for a vaccine product is inherently limited by the number of people in the population group targeted by the vaccine. A basic pediatric vaccine will be used between one and five times, depending on the schedule of inoculation, on a cohort of about 4 million children born in the United States each year.<sup>12</sup> In 2002, about 140 million units of vaccine were used for children, over one-third of which was represented by three vaccines: diphtheria, tetanus, and pertussis (known as DTaP-containing) combination vaccine (20 million doses); polio vaccine (19 million); and measles, mumps, and rubella (12 million). In contrast, prescriptions for a “blockbuster” drug like Lipitor are filled over 66 million times each year,<sup>13</sup> with annual revenues (above \$10 billion) in excess of the total worldwide vaccine industry. The potential to increase vaccine market size through international sales is limited by both disparate regulatory requirements across nations and weak purchasing power in developing countries. Therefore, the potential volume of product sales for vaccines is relatively finite and small.

**Barriers to entry** — Only a handful of suppliers are currently positioned to play in the vaccine market. High start-up costs and specialized expertise requirements restrict market participation to the limited number of entities capable of mobilizing both the significant capital and highly skilled labor necessary for vaccine development and commercial production. The high start-up costs are related to significant research and development expenses, as well as the costs associated with the construction of specialized vaccine production facilities.

The experience and infrastructure developed to produce one vaccine does not translate directly into an ability to produce a different vaccine. Existing manufacturers also face high start-up costs when launching a new vaccine product. However, manufacturers already participating in some type of vaccine production are arguably best positioned to compete in additional segments of the vaccine market. Even a well capitalized newcomer to the

vaccine industry would face significant competitive disadvantages. Vaccine production is highly dependent on skilled labor, and existing firms already command the human resources with the requisite scientific, technical, policy, and regulatory expertise.

**Competitive pressures** — If multiple members of the limited field of vaccine suppliers elect to produce substitutable vaccine products, price competition among firms with high start-up costs, high fixed costs, and relatively low variable costs will be fierce. Mercer Management Consulting calculates that only 15 percent of the costs of vaccine production are variable and change directly in relation to the amount of product made. Sixty percent of vaccine production costs are fixed, meaning they will not change regardless of how much product is produced. An additional 25 percent of production costs are semi-variable, meaning they are fixed for each batch of vaccine produced, no matter how many doses are produced per batch.<sup>14</sup>

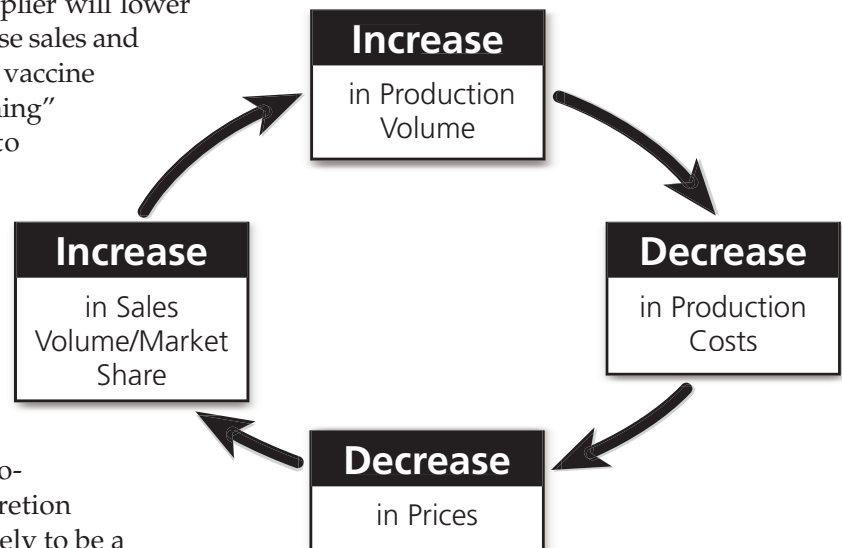
High fixed costs create powerful incentives for manufacturers to achieve economies of scale by maximizing production capacity. As the volume of vaccine produced increases, the average cost of producing each dose drops dramatically. Under these conditions, suppliers will seek to peg production capacity to anticipated demand levels and make as much vaccine as capacity will allow. The supplier will lower prices aggressively in an effort to increase sales and capture market share. As the volume of vaccine produced and sold increases, the “winning” manufacturer is increasingly able to undercut competitors’ prices, further reinforcing market dominance.<sup>15</sup>

Once the market share of a “losing” supplier falls below the level necessary to sustain the high fixed costs of continued production, the supplier is likely to exit the market. Determining what level of sustenance is required to support continued production is, at least in part, at the discretion of individual manufacturers and is likely to be a function of their profit expectations and perceived opportunity costs. Some markets may be large enough to support multiple manufacturers at their full production capacity, so a single “winner” may not emerge. However, if a monopoly does not result, the market will likely be dominated by relatively small number of producers.

Capital investment requirements may precipitate market exits. Cost increases related to changing regulatory requirements, such as the removal of the preservative thimerosal due to safety concerns, or facility maintenance expenditures to ensure compliance with existing standards, can hasten decisions to withdraw from the market. Faced with making a

### Vaccine Market: Winner(s) Take All

High fixed costs lead to intense price competition. Manufacturers seek to maximize production capacity and are willing to lower prices in order to capture market share.



significant financial investment to stay in a losing game, a manufacturer in a relatively weak market position is likely to stop production.

In the absence of patent protections, the emergence of one or few dominant suppliers occurs less frequently in pharmaceutical markets. Pharmaceutical markets are generally larger than vaccine markets relative to the fixed costs of production. Demand levels are typically robust enough to allow several suppliers to co-exist, each capturing the volume of sales necessary to sustain production costs.

The financial hit taken by the “losing” player in a vaccine market is quite substantial. Retooling vaccine production facilities to manufacture a different vaccine is very difficult and costly, and the knowledge gained through research and development efforts has limited application to other products. Therefore, the significant financial resources invested in start-up are largely sunk costs. They can not be recouped through alternative business opportunities. This makes the “winner(s) take all” vaccine market a very risky venture for would-be manufacturers.

**Price sensitivity** — Competitor withdrawal from vaccine markets makes the position of the “winning” firm or firms more attractive from a pricing perspective, but prices generally do not spiral upward even if a monopoly position is secured. The reasons for this relative stability in prices stems from the nature of demand for vaccine products. The demand factors suppressing price differ somewhat for pediatric versus adult vaccines.

Demand for childhood vaccines tends to be highly concentrated, with federal and state governments purchasing approximately 60 percent of all pediatric vaccines sold in the United States.<sup>16</sup> The purchasing power and political clout of the government has historically put downward pressure on vaccine prices. Some of this pressure has taken the form of direct, legislatively imposed price caps. However, even when explicit price controls are not in place, government purchasers have been viewed historically as inflexible customers who will demand low prices. Recent events suggest that this view may be changing (see “A Government Success Story?” on page 26) and is leading to departures from the typical market dynamic.

The purchase of adult vaccines tends to be less concentrated and less controlled by government purchasers, but demand for these products is less predictable and generally weaker relative to pediatric vaccines. Insurance coverage for adult vaccines is less common than coverage for childhood vaccines, meaning that patients are more likely to pay out of pocket for these products. Vaccines are given to healthy people, who may not fully appreciate the need for disease protection. Because the perceived need for the vaccine product is low, patients tend to be very price sensitive. Even when fully covered by insurance, uptake rates for adult vaccines are low, suggesting, at least in part, weak consumer demand for these products. Adults appear more willing to risk their own vulnerability to infectious disease than to gamble on that of their children.

Physicians and other health care providers play a very important role in mediating the demand for vaccine products. Consumers are more likely to receive a vaccine if their provider offers and recommends it. Provider payment incentives could significantly influence providers' willingness to offer vaccination services. A recent survey of obstetrician-gynecologists found that although the majority recommended influenza vaccine for pregnant women, less than 40 percent of those that recommended vaccination actually provided the vaccine through their practice.<sup>17</sup> Concerns related to reimbursement and liability were cited as the main reasons for not administering the vaccination.

Whether driven by patient, provider, or purchaser concerns, demand for vaccines is considered highly price sensitive. Relatively low vaccine prices for both childhood and adult vaccines provide little incentive for new suppliers to enter the market with similar "me too" products. An alternative manufacturer might consider launching a substitute product if that product was clearly superior in terms of safety, effectiveness, or convenience and if it promised to completely displace the existing product. This would allow the new entrant to "steal" the existing manufacturers' market share and become the new dominant supplier.

This dynamic of displacement by a superior product has played out on multiple occasions with pediatric vaccines. Many of the new formulations are broader combinations of multiple vaccines, which offer convenience to parents, children, and practitioners by reducing the number of separate inoculations required. Due in part to the market influence of recommendations issued by professional societies (such as the American Academy of Pediatrics) and the CDC-sponsored Advisory Committee on Immunization Practices (ACIP), new combination vaccines have quickly supplanted existing products in most corresponding vaccine product classes. The withdrawal of competitors' products diminishes the competitiveness of the market. This trend may have reached its limits, however, due to a variety of factors, including decreased provider revenue associated with combination vaccines.

**Inventory control** — Once established, a dominant vaccine supplier has little incentive to maintain excess production capacity or produce surplus vaccine. The high fixed costs associated with producing each batch of vaccine combined with the perishable nature of the product encourage manufacturers to closely match production volume with anticipated demand. Manufacturers are likely to be conservative in estimating market demand and, by extension, in determining production capacity because unsold inventory can significantly detract from already low profit margins.

Furthermore, because production capacity is difficult to scale incrementally, manufacturers must decide how much capacity to build long before the product is even marketed, often before Phase III trials are begun. This puts enormous pressure on manufacturers to correctly estimate demand levels. Too low an estimate will not allow the manufacturer enough



latitude to secure adequate market share, compromising its ability to win in the price competition. Too high an estimate will inflate their cost base and erode profit margins.

This tightly orchestrated match between demand and supply can lead to vaccine shortages when demand unexpectedly exceeds planned production levels, or when problems encountered in the manufacturing process diminish vaccine yield. The cost structure of vaccine production favors concentration in terms of numbers of participating manufacturers, numbers of production facilities operated by those manufacturers, and the numbers of batches run to produce the vaccine product. A single glitch in production can have a huge effect on the total available supply.

Given the complexity and unpredictability of the vaccine production processes, it is difficult to prevent such problems entirely; periodic vaccine shortages are inevitable. The influenza vaccine is particularly vulnerable to supply interruptions. Because the vaccine must be reformulated annually, the production process is less predictable than that for other vaccines, and reserves or stockpiles cannot be established to ease shortages when they occur.

Neither can production capacity be easily altered to accommodate unanticipated increases in demand or to compensate for low yields experienced in prior production cycles. The long time frames inherent in vaccine production, the capital-dependent nature of the production process, and the resources needed to meet regulatory requirements make vaccine production capacity and, consequently, supply inflexible in the short term.

### **Bigger Fish to Fry**

Entering into vaccine markets can be an unappealing business proposition for reasons beyond the “winner(s) take all” dynamic described above. While the interplay between supply costs, market size, and consumer price sensitivity clarify why established vaccine markets are typically served by one or few suppliers, they do not fully account for limited industry interest in developing novel vaccines. Why aren’t manufacturers more eager to develop new vaccines with the hopes of cornering the market on these products?

The reasons that vaccine development is often seen as a poor business investment relate in large part to how vaccines compare to pharmaceutical products. Because the major vaccine manufacturers in the United States also produce pharmaceutical products, proposals to invest in new vaccine products often compete with drug development initiatives that appear much more lucrative. In comparison to these potentially high yielding investments, vaccine development does not appear to be an attractive option.

Although investment decisions in the pharmaceutical field are highly complex, such decisions hinge on three key issues: (i) achieving profit margins

**Vaccine investments compete with drug development efforts that can appear more lucrative.**

in accordance with the external expectations of the financial/investment community, (ii) the ability to generate significant revenue (in other words, finding a market that supports sales through high prices, high volume, or both), and (iii) identifying markets with growth potential.

**Profitability** — Outside expectations factor significantly in the involvement of publicly owned drug companies in the vaccine market. Pharmaceutical companies are obligated to seek high rates of return to satisfy the expectations of their investors. Investments in ancillary businesses such as vaccines can be profitable, but if they do not match the high returns and high growth expectations of major pharmaceutical products, they will be viewed as a drag on a company's overall profitability.

Financial markets expect that publicly owned pharmaceutical firms will only invest in high growth and high profit margin areas. The chair of Wharton's Health Care Systems Department, Mark Pauley, noted that "the rules of thumb" for allocating investments within drug companies "favor the more profitable silos." Benchmarked against drugs, Pauley said, vaccines in general look like low-margin products.<sup>18</sup>

Two other recognized economists in the pharmaceutical field, Henry Grabowski and John Vernon from Duke, have argued that returns on investment in vaccines have historically lagged behind pharmaceuticals because of the large capital investment required for vaccines.<sup>19</sup> In calculating return on investment, a product's profitability is considered within the context of the time spent in achieving those returns. Because capital costs are so high and must be accrued so long before revenues are generated, vaccines compare unfavorably relative to pharmaceuticals when considered from the longer term perspective of return on investment.

**Size matters** — The limited market potential for vaccine products, as measured by total revenue, is a key reason why pharmaceutical development proposals are often seen as more appealing relative to vaccines. This market limitation is driven by both volume and price considerations. Two economists recently analyzing the underlying incentives for the development of drug treatments versus vaccines find that drugs appear to be more efficient revenue producers than vaccines.

The economists Michael Kremer of Harvard University and Christopher Snyder of George Washington University developed models and equations to elaborate on the common and intuitive view "that firms prefer treatments to vaccines since a vaccine often cures after a single dose, only allowing one chance to extract revenue from a consumer."<sup>20</sup>

Kremer and Snyder show that the effect of treating patients after they have contracted a disease changes the value of the product to patients and increases the amount that can be charged per dose compared to vaccines. Because preventative vaccines are used broadly among the population to protect people who will not be exposed to a disease as well as those who are likely to be exposed, there is an innate pressure to hold

down the per-dose price. People who are at low risk, or perceive themselves to be at low risk, of contracting the disease are not likely to value the protection highly.

Treatment products “extract revenue” from a large population “more effectively than vaccines,” according to Kremer and Snyder. “Since vaccines are administered before consumers contract the disease, there is no basis on which the firm can discriminate among” people at different levels of risk and no way for the firm to determine which consumers would be more likely to pay a high price for a product. Kremer and Snyder note that drug treatments are given to consumers after they have contracted a disease and thus the value individuals place on the product is clearer.

The economists also note that vaccines can affect long-term commercial return calculations by preventing the transmission of infectious disease. “Drug treatments allow the firm to extract rent from the whole stream of future generations; vaccines end up reducing the prevalence of the disease among future generations, in the extreme eradicating the disease from the population.” The combination of these factors make the potential revenues of drugs much greater than vaccines.

**Growth potential** — The very stability of some vaccine markets makes them unattractive to some drug companies. Historically, a prime example has been the pediatric vaccine market. The annual birth cohort in the United States has remained relatively stable for nearly a decade. Vaccination rates are approaching a saturation point (that is, approaching the positive target of nearly full vaccination of all preschool-age children for several diseases). Companies producing preschool vaccines face the prospect of manufacturing the same number of shots or vaccination doses year after year without new growth prospects. Although such a stable market may appear initially attractive, it causes problems in an industry segment that is constantly on the search for growth areas. Some manufacturers have recently begun to pursue new markets to make childhood vaccines more attractive by preparing versions of the product targeting older populations (such as developing a varicella vaccine that targets shingles as well as chickenpox) or adding “booster” dosages targeted toward adolescents.

During the recent debate over the level of incentives necessary to attract manufacturers to bioterrorism countermeasures, one vaccine company executive explained the pharmaceutical industry’s preference for long-term growth markets. At an October 27, 2004, NIH-sponsored meeting, Wyeth Executive Vice President George Siber indicated that vaccine stockpiles (even large ones for 200 to 300 million doses for bioterrorism vaccines) were not an attractive commercial proposition for major companies. Investors “want to see growth in the companies [they] invest in and a bioterrorism vaccine released to stockpile followed by a rotation of the stockpile is not a growth proposition.” Because of the one-time nature of the government’s need in this field, the Wyeth executive stated “I don’t believe we will see large industrial firms flocking to make bioterrorism vaccines.”<sup>21</sup>

These growth expectations are linked to the way stockholders value firms, influencing the price at which shares in these firms are traded. In publicly traded companies with many shareholders, stock price, rather than profitability, dictates the value of the firm. Although profit margins influence stock price, a growing firm will be more highly valued than an equally profitable firm whose growth appears to be stagnant.

### **Liability: The Straw That Broke the Camel's Back?**

Liability concerns further compromise the business appeal of vaccine production. In addition to the unforgiving nature of the market and the unfavorable financial prospects relative to pharmaceuticals, potential vaccine manufacturers also face the specter of crippling financial payouts related to product liability cases. Despite the cautious risk thresholds used by regulators in approving vaccine products, these products are particularly vulnerable to product liability suits because they are given to healthy people.

Even in cases where the link between a vaccine and adverse health events has not been scientifically established, litigation expenses, negotiated settlements, and liability insurance can significantly add to manufacturers' production costs. In the late 1980s, lawsuits totaling more than \$21 million were filed after a British researcher published a paper suggesting that the pertussis vaccine caused brain damage in some children. Although this finding did not hold up to scientific inquiry, the costs of defending against liability suits combined with some significant settlements contributed to manufacturers exiting the market and increased product costs.<sup>22</sup>

The magnitude of liability-related costs cannot be quantified precisely. Some skeptics question the degree to which liability concerns truly influence manufacturers' decisions to enter or remain in vaccine markets given the liability protections now provided under federal law. The National Vaccine Injury Compensation Program (VICP), instituted in 1986, was created to provide an alternative compensation system for individuals injured from receiving a recommended childhood vaccine. Funded through an excise tax on each dose of covered vaccine sold, the VICP has streamlined compensation for persons experiencing adverse events known to be associated with vaccines and has established a scientifically rigorous forum for considering injury causation.

Although it has reduced manufacturers' liability burden, the VICP does not fully resolve liability concerns.<sup>23</sup> Claimants can reject VICP decisions and pursue subsequent legal action through the courts, and acceptance of a VICP award may not preclude claimants from seeking compensation for pain and suffering through the tort system. In addition, VICP does not provide liability protection for all vaccines licensed for sale in the

**Some question the degree to which liability concerns influence manufacturers' decisions to enter or exit the market.**

United States. The VICP program is generally limited to vaccines routinely given to children, although some vaccines included in the program are also marketed to adults, such as the influenza vaccine.

Liability concerns reportedly played a role in GlaxoSmithKline's decision to withdraw the Lyme disease vaccine from the market.<sup>24</sup> This product was not covered by VICP, and the manufacturer spent millions of dollars defending its product against claims that the vaccine caused chronic arthritis, muscle pain, and other chronic conditions, despite the lack of sound evidence to prove these assertions. These liability concerns, combined with limited market potential, led to the product's complete withdrawal.

## POLICY INTERVENTIONS

The economic dynamics of vaccine markets and the financial calculus of vaccine manufacturers are both efficient and rational, but the existing vaccine enterprise fails to meet a range of public health objectives. Vaccine shortages threaten the health of children and adults, cause significant disruption to the operations of health care providers, and undermine public confidence in the benefits of vaccines. Vaccine products that could offer important disease protection to targeted populations have been withdrawn from the market and are no longer available. Inadequate investment in research and development has likely delayed the availability of new vaccines that could prevent death and disability.

Policy proposals to stimulate the vaccine market to correct these problems can be divided into "push" and "pull" strategies. Push strategies seek to address the supply-side issues that vex the market by lightening the burden of production costs. Pull strategies strive to improve demand-side conditions by "sweetening the pot" through increased demand volume or enhanced product prices.

### Push Proposals

Push mechanisms have been viewed as relatively weak drivers of the vaccine market.<sup>25</sup> However, it is unclear whether this finding reflects inadequate investment in push policies or an inherent failing of supply-side interventions in the vaccine context. These types of policies do require the government to intervene more directly in developing vaccine candidates and supporting manufacturer production efforts. Push strategies typically require financial investment early in product development without any guarantee that a useable vaccine will result, shifting risk from the private sector to the public sector. These issues may reduce policymakers' enthusiasm for push proposals.

From the manufacturers' perspective, push strategies improve the financial prospects of vaccine development and production but do little to guarantee the sales volume or purchase price that dictate profitability,

revenues, and growth potential. Despite these drawbacks, a number of push proposals have been pursued or proposed to enhance the stability of the vaccine market.

**Research and development subsidies** — Public funding of vaccine discovery and early development efforts can significantly reduce manufacturers' upfront financial outlays and favorably alter return on investment calculations. The NIH sponsors approximately one-third of all vaccine-related research.<sup>26</sup> The mechanisms used to distribute these NIH funds vary widely. In some cases funding is directed toward specific manufacturers who typically secure the funds through competitive applications. In other cases the research and development work is conducted by academic institutions and supported through government grants. Some research is done directly by government agencies or secured through contractual mechanisms. The results of such government-funded research are generally in the public domain for private sector entities to capitalize on as they see fit. Other models offer tax credits to companies that engage in specific types of research.

The first BioShield Act of 2004 conferred more authority and leadership in the vaccine development effort on the National Institutes of Allergy and Infectious Diseases (NIAID). The law increased the federal share of bioterrorism projects handled by NIAID and allowed the institute to confer grants to modernize biomedical capacity. NIAID has moved to the forefront of the federal government's research and development efforts in the vaccine area. NIAID has the fastest growing budget among the NIH institutes. NIAID has taken the lead in the direction of vaccine research on HIV and is involved in the planning for pandemic vaccines. The institute is on track to spend nearly one-quarter of its total budget on vaccine development: \$1.4 billion out of a total of \$4.5 billion.<sup>27</sup>

Among the range of vaccine projects in the NIAID purview are projects on the next generation anthrax vaccine (called rPA), testing on several new smallpox vaccines to lessen the side effects of those vaccinations, a human trial on an Ebola virus vaccine, continued work on AIDS vaccines, and numerous flu vaccine projects.<sup>28</sup> At the end of March 2005, NIAID selected three sites to enroll 450 healthy volunteers for a Phase I (safety) trial of Sanofi Pasteur's H5N1 avian flu vaccine.

Federally sponsored research and development has generally focused on basic research and vaccine discovery, but in some cases has extended to larger, clinical trials of vaccine candidates. NIAID recently completed construction of a Vaccine Pilot Plant in Fredrick, Maryland, that will manufacture selected candidate vaccines for the early phases of clinical trials. Some observers have argued that NIAID should focus less on the development of specific vaccines and more on finding solutions to the regulatory challenges that hinder vaccine production. For example, the lack of

**NIAID spends nearly one-quarter of its total budget on vaccine development.**

analytic technologies to characterize the end product of vaccine production necessitates costly, cumbersome, process-intensive quality assurance activities. The development of advanced analytic techniques for vaccine characterization and potency determination could significantly streamline vaccine approval and production.<sup>29</sup>

Senate bill 1873, introduced in the 109th Congress, would create the establishment of a Biomedical Advanced Research and Development Agency (BARDA) to coordinate and support the development of biodefense and pandemic influenza countermeasures, including vaccines. Some believe that the creation of such a dedicated agency is needed to mediate priorities across agencies in the Department of Health and Human Services (DHHS), as well as to create an infrastructure for more directed funding of biodefense countermeasure priorities. Concerns have been raised that NIH's traditional grant-funding mechanisms do not provide the framework needed for a "hands-on" government role in moving relevant research and development forward. Others have questioned the Freedom of Information Act exemptions that S.1873 would extend to BARDA and worry that such exemptions could hinder the open access to information that promotes good science.

**Regulatory clarification and harmonization** — In some ways the impact of governmental support for research and development is counterbalanced by stringent FDA regulatory requirements regarding product approval and manufacturing practices. The requirements promulgated by FDA have often been cited by industry representatives as a significant, and correctable, cost driver for vaccine production. Though the need for strict regulatory oversight is widely acknowledged, some observers have noted that more transparent, consistent implementation of regulatory authority could decrease production costs. Proposals to allow accelerated approval for products with high societal benefits have also been made. Such proposals would allow deemed products to utilize surrogate endpoints, such as antibody levels, in the place of clinical outcomes to demonstrate product efficacy.<sup>30</sup> Regulatory reform has also been proposed to reduce discrepancies between FDA requirements and those of foreign regulators. For example, the FDA does not allow the transfer of results from clinical trials conducted overseas to the United States if the trials have not been monitored by FDA. In contrast, FDA-monitored trials are transferable to most European countries. Improved regulatory harmonization could facilitate global distribution of a given product, allowing the high fixed costs of vaccine development to be spread most widely.

**Production subsidies** — Government funding to support production costs is less common than subsidization of vaccine discovery and development. However, several proposals have been suggested to create incentives for ongoing participation in vaccine markets. Some of these proposed production subsidies are specifically targeted at encouraging manufacturers to invest in excess or idle capacity that could be leveraged in emergency

situations when supply shortages occur. Other proposals are focused on stimulating investment in new production technologies. For example, one suggestion discussed in vaccine policy meetings and on Capitol Hill calls for tax incentives such as accelerated depreciation for upgrade investments. Tax incentives have been incorporated into two recent bills designed to stimulate development of biodefense products.<sup>31</sup>

Upgrade incentives could make corporate decisions to continue funding improvements easier, but for suppliers with overseas production facilities, such incentives may not have any value. Specifically, tax incentives for upgrades are not likely to have affected the 2004 flu vaccine shortage situation. Chiron's loss of about 50 million units of flu vaccine stemmed from quality problems at a vaccine production facility located in Liverpool, UK. Whether U.S. tax credits would have extended to foreign sources of supply is questionable. Even without specific tax credit incentives, Chiron invested more than \$70 million from 1999 to 2004 in the bulk ingredient and filling operations at Liverpool and was planning an additional \$100 million investment in increased capacity and quality controls.<sup>32</sup>

**Government production** — At the extreme of production subsidies is fully funded government production of a vaccine. Under this model, the full cost of vaccine production would be sponsored with public funds either in a government-owned and -operated facility (sometimes referred to as GoGo) or in a government-owned facility with a private entity managing operations through a contractual agreement (sometimes referred to as GoCo). This strategy has typically been proposed for vaccines that have very limited market appeal. However, full government sponsorship of vaccine production, even for a narrow subset of vaccines, has historically had limited political support. This reluctance stems from concerns related to the government's ability to operate efficiently and innovate, along with a general aversion to assuming functions that could be carried out by the private sector. Michigan and Massachusetts have sponsored vaccine production for DTP and Td (tetanus and diphtheria). These government-owned manufacturers struggled to meet the development costs for new products; Michigan eliminated and Massachusetts scaled back vaccine production activities.

**Liability protections** — There are three basic models of liability protection that appear relevant to the vaccine discussion. Compensation programs established for required general use vaccines, such as the VICP, offer one approach. A compensation plan essentially deflects litigation from the courts; it requires a specific set-aside of funds to pay claims that are adjudicated through administrative mechanisms. Such programs do not necessarily shelter manufacturers from suits; the tort system remains a fallback option for claimants. Compensation programs can lessen the cost burden of litigation by weeding out the majority of cases, can spread award-related costs across time, and may shift some liability to

## Full government sponsorship of vaccine production has had limited political support.



purchasers through an excise tax mechanism. Such programs may also impose more rigorous scientific scrutiny in settling claims, which may influence award levels. Even if the claimant pursues subsequent legal action, the scientific evidence compiled through the administrative process can be brought to bear in tort proceedings.

Tort reform approaches have also been used to protect manufacturers of products that are required for general use by the population or a segment of the population. These policy proposals seek to indemnify the manufacturer against liability risk, but typically include exceptions for cases of willful misconduct. This form of tort reform was embodied in the Swine Flu program in 1976, was applied to smallpox countermeasures under Section 304 of the 2002 Homeland Security Act (P.L. 107-296), and more recently was extended to pandemic influenza vaccines and countermeasures in fiscal year 2006 DoD appropriations. These types of liability protections effectively transfer liability from vaccine manufacturers and administrators to the federal government.<sup>33</sup>

A related form of liability protection also embodied in the Homeland Security Act is a government contractor's defense under the Federal Tort Claims Act. This approach appears in Section 863 of the Homeland Security Act to cover antiterror technologies used in response to an attack. Statutory language can extend Federal Tort Claims Act protections to private sector individuals or organizations acting on behalf of the government. Because vaccines are often used as a prophylactic, this provision of the Homeland Security Act may require revision to be appropriate for bioterrorism preparedness vaccines.

## Pull Proposals

Pull strategies are perhaps more common than push strategies, but they too are not without controversy. Pull proposals are inherently an attempt to manipulate demand. In theory, government intervention serves to augment demand, creating a more attractive market for potential investors. Government subsidies for vaccine purchases are perhaps the most common, and the most hotly debated, type of pull mechanism.

Government purchase of vaccine products as attempts to enhance the market appeal of vaccines can be a double-edged sword. Government purchase commitments can significantly increase the level and predictability of demand for a vaccine product. But many observers believe that these increases in sales volume are undercut by the lower prices demanded by government purchasers. The recent product launches in the childhood vaccine market suggest, however, that under certain conditions, the power of government purchasers to negotiate price can be limited enough to provide a net market incentive, as with the Vaccines for Children Program (VFC) (see sidebar, next page). Absent explicit, statutory price caps, government purchase may serve as a positive stimulus to vaccine development and production.

Because of concerns regarding pricing distortions, new proposals to expand government purchase commitments have generally been designed as supplements to the private vaccine market. Where significant commercial markets exist, alternative pull proposals that boost demand levels, while leaving price negotiations to decentralized private purchasers, may be more appealing to manufacturers. The following reviews some of the pull strategies currently used, or proposed, to improve vaccine market dynamics.

**Stockpiles** — Stockpiles are, put simply, an artificial enhancement to current market demand levels in anticipation of periods when supply will be insufficient to meet demand. For example, stockpiles of smallpox vaccine provide a safeguard should smallpox be used as a bioterrorism agent. Such forward-thinking planning is driven by concerns related to the likelihood of future disruptions in vaccine production or expectations that the threat of a given infectious disease will increase significantly at some point in the future. Government funding of vendor-managed stockpiles of childhood vaccines ensure that some excess vaccine supply is always available to buffer supply problems when they occur.

The volume and pricing of stockpile purchases differ significantly for products that are presently sold in private markets compared to products that have no current commercial value (that is, where the government

Continued, page 28 ►

## A Government Success Story?

Major new vaccines are entering the market as significant commercial and public health successes. Prevnar, Wyeth's childhood pneumococcal conjugate vaccine, is a particularly eye-catching example. Approximately 65 million units of the product were distributed in the first four and one-half years of use in the United States. Rates for Prevnar vaccination\* reached 68.1 percent in 2003, the product's third year of availability in the U.S. market.†

This fast uptake for a product with the relatively limited target population—children under 4 years of age—was achieved despite almost three years of supply shortages and a steep introductory price of \$58.00 per unit at full list price. The shortage periods (August 2001 to May 2003 and February to August 2004), in fact, were probably caused in part by stresses experienced by Wyeth while trying to keep up with higher-than-anticipated demand. The high price associated with the pneumococcal conjugate vaccine has attracted the attention of competitors as well.

GlaxoSmithKline has indicated that it plans to launch an pneumococcal vaccine within the next five years,‡ a dramatic departure from the traditional vaccine market dynamic.

Vaccinating young children with Prevnar is creating rapid spillover benefits to other segments of the population. Within three years of introduction, studies appeared indicating a "herd immunity" benefit from the pediatric use of Prevnar. "Herd immunity" is the phrase used by public health officials and the vaccine community to describe the protection provided to

Success Story / continued ►

\* For three of the recommended four shots.

† "Prevnar - first blockbuster vaccine of the millennium," Phacilitate; accessed September 2004 at [www.phacilitate.co.uk/pages/phaciliate/article\\_prevnar\\_reilly.html](http://www.phacilitate.co.uk/pages/phaciliate/article_prevnar_reilly.html).

‡ GlaxoSmithKline, "GlaxoSmithKline reviews pipeline of novel vaccines with the potential to dramatically improve global health," press release, June 30, 2005; available at [www.gsk.com/Controller/Servlet?appld=4&pageId=402&newsid=601](http://www.gsk.com/Controller/Servlet?appld=4&pageId=402&newsid=601).

**Success Story** / continued

large segments of a community by the immunization of parts of the population.

Although the public health benefits of Prevnar are now clear, the product's price nearly doubled the cost of vaccinating a child in the United States. The rapid uptake of the product, despite the relatively high price, can be traced in part to the Vaccine for Children Program. VFC was not conceived as a stimulus to the industry; it was designed to help pay for vaccinations (for the product itself and for the delivery of vaccine) to disadvantaged children. In fact, the VFC program was not warmly received by the vaccine industry when it was debated on Capitol Hill.

The industry was concerned that the program would consolidate too much of the market under the federal government and would lead to stultifying price controls. As part of the eventual political compromise that won enactment, VFC vaccines were limited to uninsured children, children on Medicaid, American Indians/Alaska Natives, and underinsured children who would receive vaccinations at federally qualified health centers.<sup>§</sup> Price controls established at the program's inception did not apply to new vaccines developed after enactment.

The impact of VFC on the purchase of childhood vaccines has been significant. Since the VFC program's inception in 1994, the share of government (federal, state, and local) purchase of childhood vaccines has risen from 35 percent of all purchases to 57 percent. In 2002, VFC purchases alone accounted for 41 percent of childhood vaccine purchases. The other 16 percent of purchases controlled by the government comes from grants from Section 317 of the Public Health Service Act (11 percent) and state and local programs (5 percent). The size of VFC vaccine expenditures has increased sharply from \$500,000 in 1994, the first year, to \$1.2 billion in fiscal 2004.\*\*

Prevnar is just one example in a growing list of new vaccines targeting the pediatric market. The continued effort and interest by major vaccine

companies to launch new pediatric products appears to be a clear sign that the incentive of a broad, subsidized market in pediatric vaccines is working. That success comes with one important proviso: the companies are expending the most effort on products for which they do not face price restrictions. The VFC program is unusual in that a scientific advisory committee, the Centers for Disease Control's Advisory Committee on Immunization Practices (ACIP), makes a recommendation that leads directly to coverage for the vaccine as a benefit entitlement.<sup>††</sup> Cost considerations are secondary to health benefits in the ACIP's process. ACIP recommendations effectively create a "must-buy" position for VFC purchasers, constraining their negotiating power.

It is not clear whether this combination of a public health review and near automatic government payment can be sustainable for a long period of time or transferable to other vaccine markets. In addition to adding to federal budgetary pressures, the ability of vaccine firms to price aggressively for new pediatric products also puts pressure on nonfederal purchasers, including state purchasers and private practitioners. In 2003, the per-dose cost of Prevnar for the private pay market was \$58.75, with the federal government negotiating a preferential price of \$45.99.

The twin incentives of the VFC market enhancement and the protections from the National Vaccine Injury Compensation Program have acted to make

**Success Story** / continued ►

§ Institute of Medicine, *Financing Vaccines in the 21st Century*, 82.

¶ A. R. Hinman, W. A. Orenstein, and L. Rodewald, "Financing Immunization in the United States," *Clinical Infectious Diseases*, (May 15, 2004): 1440–1446.

\*\* Linda Demkovich, "Vaccines for Children: Investment in Immunizations Yields Big Dividends," *National Conference of State Legislatures*, 2005, available at [www.ncsl.org/programs/health/vaccines.htm](http://www.ncsl.org/programs/health/vaccines.htm); Stephen Cochi, "National Immunization Program Report," presentation to Advisory Committee on Immunization Practices meeting, Atlanta, Georgia, February 25, 2004, available at [www.cdc.gov/nip/ACIP/minutes/acip-min-feb04.pdf](http://www.cdc.gov/nip/ACIP/minutes/acip-min-feb04.pdf).

†† Hinman, Orenstein, and Rodewald, "Financing Immunization," 1442.

**Success Story** / continued

childhood vaccines very attractive to vaccine companies. Manufacturers are pursuing products for diseases with relatively low prevalence levels and are still securing relatively high prices for the new products. In the vaccine field, one measure of value assessment

is the benefit-cost ratio. A high ratio indicates a high benefit in reduced disease for a relatively low cost. Inversely, a low benefit-cost ratio indicates that it takes higher expenditures on a vaccine to generate the benefits.

One assessment of pediatric vaccines in 2001 indicated that ratios for three new vaccines were well below older ones. Three recent benefit-cost calculations for varicella vaccine estimate a benefit-cost ratio of approximately 5:1; Hepatitis A has a benefit-cost ratio of 2:1; and two calculations for pneumococcal conjugate show ratios near 1:1. By comparison, a separate benefit-cost analysis of the older MMR vaccine come in at over 23:1. The evolution of vaccine development from diseases with historically high prevalence to diseases with lower rates of occurrence or less severity is a point of concern to some public health officials. The new vaccines are expensive and add substantially to the

Vaccine	Benefit-Cost Ratio
Measles/Mumps/Rubella	23:1
Varicella	5:1
Hepatitis A	2:1
Pneumococcal conjugate	1:1

overall cost of the standard schedule of vaccinations while arguably conferring fewer benefits (see chart).

At a National Vaccine Advisory Committee meeting in June 2004, a spokesman for the Institute of Medicine's Committee on Evaluation

of Vaccine Purchase Financing in the United States noted that there are growing concerns about the long-term budget effect of broad government coverage and recommendations for use of new pediatric vaccines without a careful, systematic review of product cost. Mark Pauly, a committee member from the Wharton health systems faculty, noted that "economists worry about unchecked behavior, of a recommendation for a relatively small benefit if someone else is paying the cost."<sup>‡‡</sup> To address that fundamental concern, the IoM committee in its 2003 report "Financing Vaccines in the 21st Century" urged the government's decision-making body for recommending vaccine use (currently ACIP) to "consider both benefits and costs" when making general use recommendations. ■

<sup>‡‡</sup> Mark Pauly, presentation to a meeting co-sponsored by the National Vaccine Program Office and the National Vaccine Advisory Committee, Washington, DC, June 28–29, 2004.

► **Continued** from page 26

represents the only buyer for the product). In the former case, such stockpiles are clearly a tool used to smooth temporary misalignment between supply and demand). The stockpile can be relatively small and pricing marginal. Stock can be rotated into circulation as expiration dates near. In cases where the product has no commercial value, stockpiles must be large enough to fully support future demand expectation, prices must be attractive enough to encourage vaccine production independent of other buyers, and the costs of stockpile replenishment cannot be offset by the sale of rotated product.

**Advance purchase agreements** — Government guarantees to purchase a specified volume of vaccine at a specified price can encourage manufacturers to expand production capacity or stimulate investment in new

vaccine development. Again, such agreements are most attractive to industry if they do not erode or jeopardize sales in the more lucrative private market. Government guarantees to purchase unused influenza vaccine inventory have encouraged manufacturers to ramp up production capacity, despite yearly fluctuations in consumer demand. Similarly, advance purchase agreements have been proposed to encourage development of vaccines directed against diseases that are prevalent primarily in developing countries. Public and philanthropic commitments to purchase these vaccines assure the manufacturer of a paying buyer. Absent these commitments, the need for the product would still exist but the economically supported demand would not.

**Coverage through public insurance programs** — Coverage of vaccine products through public insurance programs clearly increases the demand for these products. While childhood vaccines are both covered and purchased centrally for Medicaid through the Vaccines for Children program, coverage decisions related to adult vaccines are left to the discretion of individual states, which can negotiate purchase prices.

In contrast, purchase prices for Medicare-covered vaccines are negotiated by health care providers in a decentralized fashion (although coverage decisions are made at the national level through legislative action). The Government Accountability Office has estimated that as much as 85 percent of annual purchases of influenza vaccine occur in the private sector.<sup>34</sup> Although government involvement in vaccine purchase (either directly or indirectly) may influence prices, coverage through public insurance programs clearly increases demand levels and can make vaccine markets more appealing.

The National Vaccine Advisory Committee has called for broader public sponsorship of vaccines for uninsured adults in response to the Institute of Medicine's (IOM's) 2003 review of vaccine financing. In a summary of key recommendations for vaccine funding issued by NVAC in early October 2004, an NVAC workgroup urged "expanded discussion about need, desirability, and feasibility" of a Vaccines for Adults program "to ensure that adults have access to vaccines, regardless of whether they have insurance."<sup>35</sup> This proposal would represent a major expansion of health entitlement benefits and could be extended to the large, undervaccinated population between 19 and 65 years of age. Such an expansion could create a market stimulus parallel to that demonstrated by the VFC program.

**Universal coverage through federal purchase** — Public funding of vaccines could be extended beyond existing public insurance programs (or even beyond the incremental addition of more people to these programs through new eligibility criteria), to include the entire U.S. population. Such a strategy would likely be very controversial for vaccines currently sold in private markets, in light of the potential impact such consolidation of purchasing power might have on product pricing. However, in circumstances where private markets might be seen as infeasible—for

**Some proposals have called for broader public sponsorship of vaccines for uninsured adults.**

example in the case of a pandemic influenza vaccine—full government purchase may be needed to stimulate early vaccine development and target vaccine to priority groups.

The Institute of Medicine has proposed a universal vaccine coverage strategy that seeks to tie vaccine pricing explicitly to the societal value of specific products. This pricing scheme would, in essence, require the government to pay a premium for products that have significant public health benefits. Although government purchasers would likely pay more for the vaccine than they might if current price negotiation practices were employed, such a pricing mechanism has the potential to assure more stable supply for a broader variety of products. This recommendation was recognized as a bold break from current practice by the issuing IOM Committee. While the recommendation generated some debate, it did not generate political consideration when released.

In theory, premium pricing by government purchasers could be further expanded to the global vaccine market, with industrialized nations explicitly subsidizing the cost of producing vaccine sold in the developing world. This type of mechanism could be particularly relevant for a future HIV/AIDS vaccine, which has commercial potential in the United States and Europe but less paying demand in areas of the world with the greatest disease burden. Manufacturers' interest in moving a product past the vaccine discovery stage toward development and ultimately product approval, may be dampened by concerns that political pressures will severely constrain price, both domestically and globally. At the same time, an effective HIV/AIDS vaccine threatens revenue related to the sale of antiretroviral treatments, further weakening the business case for vaccine investments. Government guarantees to purchase the product at premium pricing has the potential to address these legitimate financial interests.

**Usage recommendations or mandates** — Even when government is not directly involved in vaccine purchase decisions, government policies can have a dramatic impact on vaccine demand. The vaccination recommendations promulgated by government-sponsored advisory bodies, such as the ACIP, can be tremendously influential in determining the policies of professional societies, like the American Academy of Pediatrics, and in directly encouraging health care providers and consumers to utilize a particular vaccine product. In some cases, government mandates related to vaccination requirements for admission to public schools or foreign travel can also significantly affect the demand for particular vaccines. While school-related vaccine policies are more commonly made at the state and local level, federal guidance and funding conditions can be very important factors in these decisions. Social marketing campaigns to improve public understanding and acceptance of these recommendations and mandates can also increase demand.

**Injury compensation programs** — Although compensation programs are usually viewed as a component of the “push” strategy to limit manufacturers' liability costs, such programs also serve as a “pull” mechanism by

increasing consumers' willingness to be vaccinated. Assurances that compensation will be forthcoming if a vaccine-related injury is sustained may increase demand by encouraging consumers to comply with vaccine recommendations. Such encouragement is perhaps most important for vaccines where the consumer has a high degree of latitude in choosing whether to be vaccinated and a low perceived risk regarding the disease threat targeted by the vaccine. For example, some believe that participation of health care providers in the recent campaign to inoculate first responders against smallpox was negatively influenced by delays in establishing compensation provisions.

**Insurance mandates** — State and federal mandates that require insurers to cover particular vaccines can have a significant impact on consumer demand for these products. Insurance mandates reduce out-of-pocket expenses for consumers and significantly decrease the financial barriers to vaccine uptake. However, constraints related to ERISA (the Employee Retirement Income Security Act) may diminish the effect of federal policies in this regard.

**Market exclusivity** — Strategies that seek to strengthen the intellectual property rights associated with vaccine development do not increase demand levels per se, but they do guarantee that the innovating manufacturer will fully capture existing demand. The models for market exclusivity incentives are based on the existing programs for orphan drugs (the Orphan Drug Act, P.L. 97-414) and pediatric drug testing (Best Pharmaceuticals for Children Act, P.L. 107-109). The fundamental idea is that companies undertaking research on particular types of products (such as bioterror countermeasures, including vaccines) could extend the period of exclusive marketing rights provided under patent law.

Due in part to the problematic nature of patent protections in the vaccine field, modifications of this approach have been proposed. Some proposed policies would provide for market exclusivity protection outside of the patent framework, others would offer "wild card" patent extensions to alternative products in the manufacturer's portfolio. Such wild card provisions are a very attractive stimulus to large pharmaceutical companies. Companies that received wild card extensions for bioterrorism work could get an immediate payback from continued sales and profits from large, established products. The extensions would carry a potentially high cost to society through private and public purchasers in the form of longer periods of premium pricing for successful drugs. As a major purchaser of drugs through many programs (Medicaid, Medicare, Veterans Affairs, and Department of Defense), the federal government would absorb the higher costs from wild card extensions. In effect, such provisions would provide an indirect and "off budget" subsidy for bioterrorism research.

The intellectual property incentives appear to be most attractive to new companies considering entering the vaccine field. Some large established

**Intellectual property incentives appear most attractive to new companies entering the vaccine field.**

vaccine companies have indicated, however, that patent extensions might be a less attractive incentive than enhanced liability protections.<sup>36</sup>

Important issues to be resolved regarding intellectual property stimuli schemes include the types of firms that could qualify for the extended protections, the point in product development at which enhanced market rights would be bestowed, the length of extensions, and the number of extensions that could be applied to specific products.

## CONCLUSION

In general, push and pull strategies share one common characteristic: governmental resources are mobilized to ensure that vaccine markets function in a manner consistent with public health goals. Although these strategies and their models differ significantly, most entail government financial support in one form or another to stimulate the vaccine market. The policy challenges lie in identifying which disease threats merit government investment in vaccine development and production, selecting market support strategies specifically appropriate for each vaccine product or candidate identified, and determining what level of resources is needed to create effective incentives.

Scientific, demographic, economic, and political realities will converge differently for different vaccines. For this reason, difficult policy decisions will likely need to be made on a vaccine-by-vaccine basis. For some vaccines, such as pediatric vaccines that are also used in the general population, additional policy interventions may not be necessary. For others, increased supports may be needed. The potential societal value of a specific vaccine or vaccine candidate, the degree to which market mechanisms are failing to achieve this potential and the political will needed to mobilize corrective public resources must be considered and balanced against each other. A clearer framework for measuring the success of this balancing act will encourage rational investments and workable interventions.

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