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Influenza Vaccine Manufacturing

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Prepared for

Amy Nevel, MPH
Senior Public Health Policy Analyst
Office of Science and Data Policy
Assistant Secretary for Planning and Evaluation
Department of Health and Human Services
Mail Stop 445F
200 Independence Ave., SW
Washington DC 20201

Prepared by

Christine Layton, PhD, MPH
Nancy Lenfestey, MHA
RTI International*
Health, Social, and Economics Research
Research Triangle Park, NC 27709

*RTI International is a trade name of Research Triangle Institute.

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This issue brief is one of five produced for the Assistant Secretary for Planning and Evaluation (ASPE) by RTI International. The contents of these briefs is based on research involving a review of literature including peer-reviewed journals, media reports, and other nonreferenced sources (including those identified using the World Wide Web search engine Google) as well as confidential interviews with 30 key informants representing influenza vaccine manufacturers, wholesalers, community immunizers, state and local public health officials, and other experts. The other briefs in the series are

- *Influenza Vaccine Economics*
- *Influenza Vaccine: Who Buys It and Who Sells It*
- *Influenza Vaccine Demand: The Chicken and the Egg*
- *Influenza Vaccine Overview: Summary and Assessment*.

This issue brief was written by Christine Layton, PhD, MPH, and Nancy Lenfestey, MHA.

INFLUENZA VACCINE MANUFACTURING

ISSUE BRIEF

1. Introduction

Influenza vaccine manufacturers have experienced intense scrutiny in recent years. Uncertain demand, short turnaround in vaccine production, evolving regulatory requirements, rising production costs, and mergers and acquisitions represent a few of the challenges facing manufacturers in this dynamically changing industry. This issue brief provides an overview of the following areas:

- § key issues facing influenza vaccine manufacturers;
- § biology of the influenza virus and history of influenza vaccination;
- § influenza manufacturing process;
- § structure of the industry and nature of the influenza vaccine market; and
- § factors that influence manufacturer decision making—quantity of vaccine produced, investments in new technologies, and entry into and exit from the U.S. influenza vaccine market.

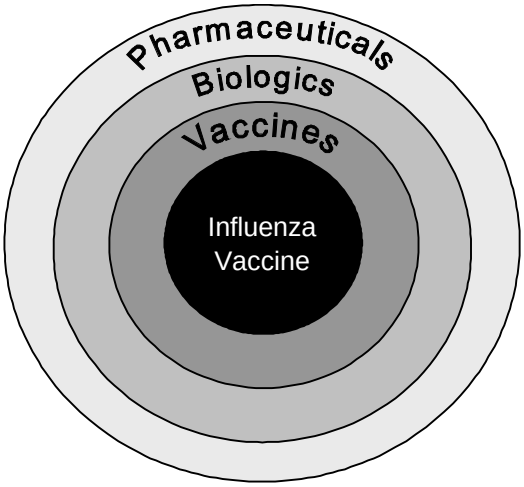
2. Key Issues Facing Influenza Vaccine Manufacturers

Vaccines are different from pharmaceuticals (Figure 1). As one key informant explained, "… manufacturing the vaccine [is] not just like turning on a spigot and some chemicals come out and you can stamp out some pills." Among vaccines, influenza vaccine is unique in that

- § influenza vaccines are reformulated each year to match the circulating strain(s) of virus anticipated in the upcoming season;
- § due to annual reformulation, influenza vaccines expire at the end of each influenza season; and
- § influenza vaccines have typically been administered prior to the start of the influenza season (approximately October–December).

The seasonality of the vaccine and need for annual reformulation contributes to the widely perceived precarious nature associated with the influenza vaccine manufacturing industry. Limited profitability when compared to pharmaceuticals and financial vulnerability stemming from unpredictable demand pose tremendous risks to manufacturers in the market. Additional discussion of these risks and challenges are noted in subsequent sections of this brief.

Figure 1. Influenza Vaccine is Unique



3. Brief Biology of Influenza and History of Influenza Vaccination

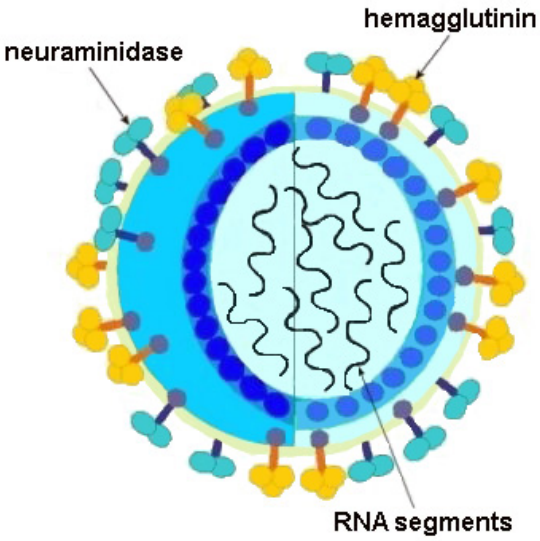
3.1 The ABCs of "Flu"

Influenza is an infectious disease that occurs primarily in the winter months in the northern hemisphere. Although influenza is often thought to be a mild illness, it causes an average of 226,000 hospitalizations (Thompson et al., 2004) and 36,000 deaths annually (Thompson et al., 2003).

Three types of influenza can infect humans: A, B and C. Influenza A causes regular outbreaks—most notably pandemics—and can also cause disease in some livestock (pigs, horses, chickens, and ducks) and some wild birds. Influenza B most often creates sporadic outbreaks among groups most at risk of influenza-related complications (e.g., residents of nursing homes). Influenza C is widespread, but does not commonly cause symptoms.

Influenza viruses are further identified by the proteins on the viruses' exterior. These proteins are neuraminidase (N) and hemagglutinin (H), shown in Figure 2. Strains of the influenza virus are generally distinguished by these exterior proteins. Three types of hemagglutinin (H1, H2, and H3), and two types of neuraminidase (N1 and N2) are generally associated with outbreaks of influenza in humans. Such nomenclature results in strains being defined with names such as influenza type A, H3N2, which has been circulating in recent years.

Figure 2. Influenza Virus Showing Neuraminidase and Hemagglutinin on Exterior



Source: Hessische Intellectual Property Offensive, n.d. Used with permission.

3.2 Drifting and Shifting

Like other viruses, influenza undergoes frequent genetic mutations. Depending on the degree to which the virus mutates, it is described as "antigenic drift" or "antigenic shift." Antigenic drift is a gradual process in which surface proteins (the antigens) are added to the virus. As a consequence, the antibodies in the animals (and humans) that developed following previous vaccination or exposure to influenza virus—in response to specific surface proteins—cannot protect the body because they do not "recognize" the altered virus, and infection and viral replication may occur. This process of antigenic drift is the major reason why it is necessary to create a new influenza vaccine every year—to ensure that the vaccine will most accurately match the virus strain circulating in a given year.

Antigenic shift is a more abrupt, major change that can occur in influenza A viruses.[1] In antigenic shift, a new hemagglutinin and/or neuraminidase protein occurs. When this happens, animals (and humans) have little or no innate protection against the new influenza virus. Pandemics, world-wide disease outbreaks, are associated with antigenic shift. In 1918, a "Spanish Flu" pandemic was associated with an H1N1 influenza virus. In 1957, the "Asian Flu" pandemic was associated with an H2N2 influenza virus. In 1968, the "Hong Kong Flu" pandemic was associated with an H3N2 influenza virus.

[1] Influenza A viruses undergo antigenic drift and shift; Influenza B viruses undergo only antigenic drift.

3.3 History of Influenza Vaccination

Scientists have attempted to control infectious diseases since the 1700s. Nevertheless, it was not until around 1930 that the viral cause of influenza was identified (Sanofi Pasteur, 2005). Development of the influenza vaccine is credited to a team effort between Drs. Thomas Francis, Jr. (1900–1969) and Jonas Salk (1914–1995). While serving as a professor and chair of the Department of Bacteriology at the New York University College of Medicine in 1938, Dr. Francis, a physician, virologist, and epidemiologist, began working with Salk (a medical student at the time), and became the first American to isolate the human influenza virus. In 1941, Dr. Francis was appointed director of the Commission on Influenza of the United States Army Epidemiological Board. Together with Salk, the two researchers made important contributions to the successful development, field trial, and evaluation of protective influenza vaccines used in the armed forces during World War II. Public health experts feared a repeat of the influenza epidemic of 1918–1919; however, development of the vaccine controlled the spread of influenza, thereby preventing another public health catastrophe (Centers for Disease Control and Prevention [CDC], 2005a; Academy of Achievement, 2005). Influenza vaccine was not commercialized in the United States until 1945 (Sanofi Pasteur, 2005).

4. Influenza Vaccine Manufacturing 101

4.1 Influenza Vaccine Manufacturing Process

Two types of influenza vaccine are licensed for use in the United States: trivalent inactivated influenza vaccines (TIVs) contain fragments of viral proteins (the Hs and Ns), and live attenuated influenza vaccines (LAIV) use the whole virus, which has been weakened. Although these two vaccine types produce similar immunity against influenza, they are approved by the U.S. Food and Drug Administration (FDA) for different groups, and different manufacturers' products are approved for use among different age groups. Table 1 shows that only one vaccine licensed in the United States is currently approved for use among all age groups.

As previously noted, fluctuations in which strains of influenza are most common require production of a new vaccine each year. Production of influenza vaccines follows a very stringent timeline. During late winter, the FDA's Vaccines and Related Biologic Products Advisory Committee (VRPAC), uses guidance from the National Vaccine Advisory Committee (NVAC) and surveillance information from the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) to select the three strains that will be included in the following season's influenza vaccine. CDC monitors and identifies the three strains (two A and

Table 1. U.S.-Licensed Influenza Vaccines for 2005–2006

Vaccine Type	Product (Manufacturer)	Approved Age of Recipient					No. of Projected Doses
		6 months–3 years	4 years	5–17 years	18–49 years	50+ years	
Inactivated	Fluarix (GSK)				X	X	8M
	Fluvirin (Chiron)		X	X	X	X	18-26M
	FluZone (Sanofi Pasteur)[a]	X	X	X	X	X	60M
LAIV	FluMist (MedImmune)[b]			X	X		3M

[a] In 2004, Sanofi merged with Aventis Pasteur to create the Sanofi Aventis Group. The vaccine division of the Sanofi Aventis Group changed its name to Sanofi Pasteur.

[b] FluMist is approved for use among those 5 to 49 years of age who are otherwise healthy and not pregnant.

Source: CDC, 2005c.

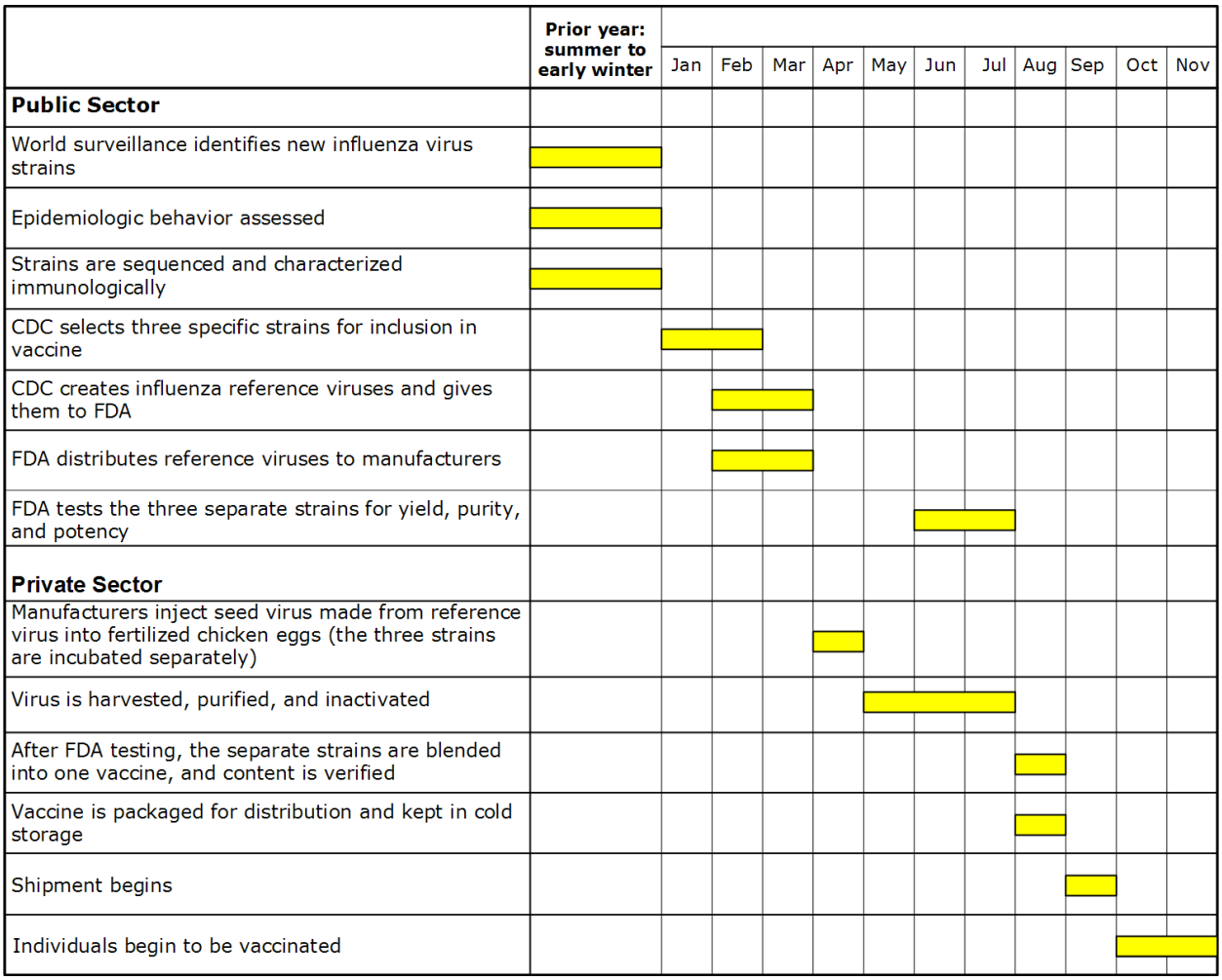
one B strain) predicted to cause serious illness in the United States during the following winter (Lister, 2004).

Because inactivated influenza vaccines make up the majority of influenza vaccine produced for the U.S. market, our description of the influenza vaccine manufacturing processes will focus on inactivated influenza vaccine. However, it is important to note that the timeline for LAIV production is similar to that of the inactivated vaccine (see Figure 3). This process is illustrated in Figure 4.

The vaccine manufacturing process can be summarized by the following phases:

§ **January–May.** CDC provides influenza reference viruses to FDA, which in turn distributes them to manufacturers. From the reference viruses, manufacturers create seed viruses, which are adapted to replicate efficiently in the manufacturer's production process. Large amounts of the influenza virus are prepared for vaccine production by injecting each seed virus in fertilized chicken eggs. To satisfy FDA requirements and ensure the safety and efficacy of the vaccine, the eggs are specially produced, assuring that appropriate precautionary measures are taken with regard to sanitation, transportation, and incubation. Upon incubation and sufficient growth of the virus within the eggs over a period of several weeks, the eggshell is opened and the egg white is removed to harvest the virus. Harvested egg fluids are then processed to concentrate, purify, and inactivate the virus (Wareing & Tannock, 2001). Each egg produces one to two doses of vaccine. Additional measures are taken to purify and standardize vaccine potency (Salinsky, 2004; Lister, 2004; Influenza.com, n.d.).

Figure 3. Timeline of the Vaccine Manufacturing Process

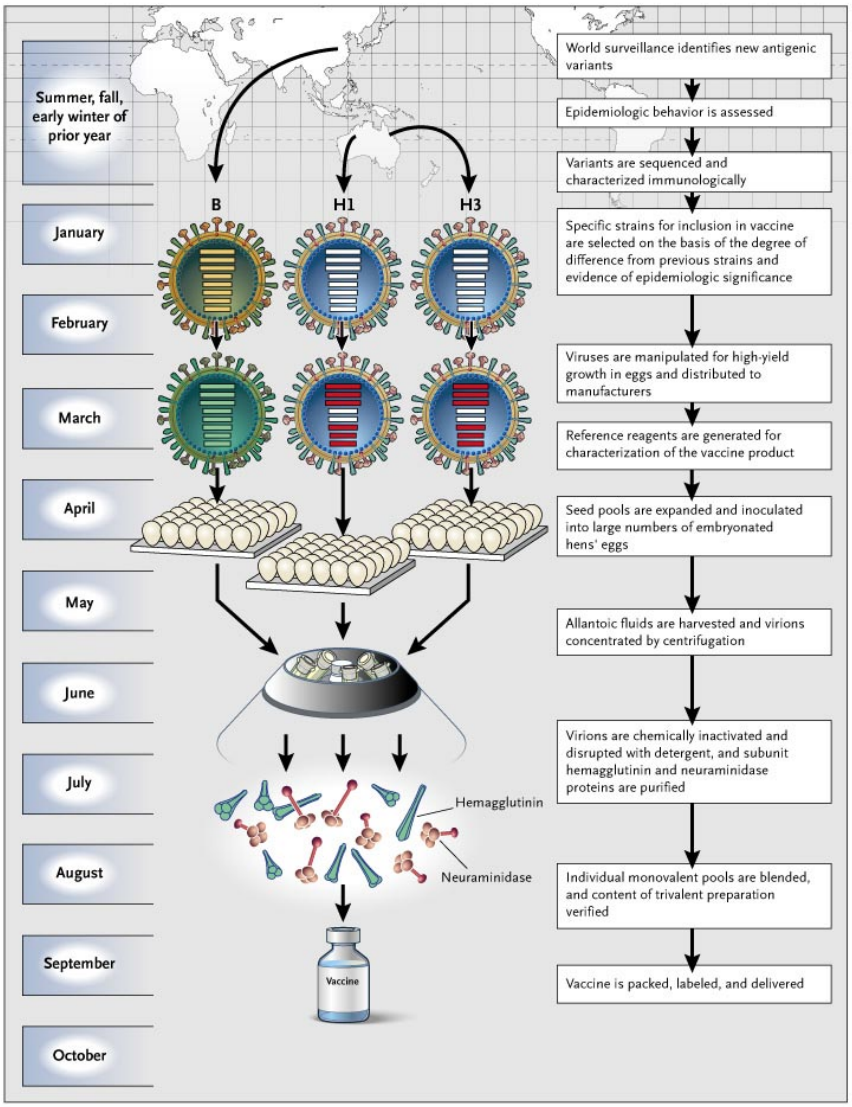


- **June–July.** FDA tests each manufacturer's strains to determine the yield of the virus, ensure its purity, and determine that the potency is sufficient for immunization. The three separate strains are then combined into one, and vials and syringes are filled.
- **August.** The vaccine is packaged and stored in cold temperatures for shipment, usually in beginning in September.
- **October–November.** Vaccinations are made available to the public. Immunity develops approximately 2 weeks after vaccination (Influenza.com, n.d.).

One manufacturer provided the following summary of the manufacturing timeline:

We need to know and be done with the order of all those things [ordering of eggs and supplies, filling, packaging, and testing] by the end of July. We'll do the egg piece through the first half of August, and then we need 2 to 3 weeks in advance to have ordered those eggs. Typically we're done with the egg piece sometime in early August

Figure 4. Vaccine Manufacturing Process



Source: Treanor, (2004). Used with permission.

> *and then we continue to fill, finish, and release throughout October and November. If you keep going later and later, you start impacting the start for the next season. We stop producing in November and we usually pick the strains for the next season in December.*

Once the influenza vaccine for a given season is made, manufacturing facilities require time to prepare for the next season. As one key informant explained

> *We also need a few weeks to shut down the plant for cleaning and maintenance. You can't run it 24-7 without having to do maintenance, that's why it's risky.*

In interviews, key informants repeatedly commented on the complexity of the influenza vaccine manufacturing process and its vulnerability to challenges, which include but are not limited to the following:

- The number of eggs required to produce the number of doses expected by the market must be estimated approximately 6 months before inoculation with the vaccine seed. (Lister, 2004; Salinsky, 2004).
- Manufacturers face the challenge of successfully growing the virus while avoiding the growth of other contaminants (Lister, 2004).
- Quantifying the new antigens may become a critical bottleneck in the production cycle since it requires several complicated steps late in the production process (Gerdil, 2003).
- Problems in which new strains fail to grow sufficiently in the eggs can result in production delays (Salinsky, 2004).
- Some strains of influenza (most notably avian influenza) are lethal to birds and therefore will not grown in chicken eggs.

In essence, making influenza vaccine is a highly complicated process involving biological components that offer less control than other pharmaceutical products. As one manufacturer explained,

> *… These are living organisms that sometimes behave differently. It's like one year you grow some tomatoes and they look great and the next year conditions may change, and it's a living organism and you may not have such great tomatoes. It's not that easy; it's very complex to manufacture biologics.*

4.2 Structure of the Industry

4.2.1 History of the Vaccine Market

Edward Jenner, a physician from the British countryside, is credited with performing the world's first vaccination in 1796. Jenner used pus from a cowpox lesion on a milkmaid's hand to successfully inoculate an 8-year-old boy against smallpox. This discovery laid the scientific foundation for modern vaccinology.

As acceptance of Jenner's discoveries became widespread across Europe, kings and presidents considered vaccines a matter of national pride and enthusiastically endorsed large-scale vaccination campaigns to demonstrate their progressive thinking and commitment to promoting the health of their subjects. However, the societal value of vaccines was soon recognized for their impact on national security and productivity. Awareness of the benefits of

vaccines led to mandatory vaccination in numerous countries. Smallpox vaccination became a requirement in Europe and North America during the 19th century, and a series of childhood vaccinations became obligatory for attending public schools in the 20th century (Stern & Markel, 2005). The last indigenous case of smallpox occurred in 1977, making smallpox the first disease eradicated from the globe by immunization (Fenner, 1988).

Despite vaccines' capacity to not only prevent but eradicate some diseases, many pharmaceutical and biotechnology companies have avoided or discontinued the manufacturing of vaccines because of current economic and regulatory hurdles (Stern & Markel, 2005). Over the past 50 years, pharmaceutical companies have acquired companies primarily devoted to the manufacture of vaccines, including Lederle and Praxis (Offit, 2005). The dwindling number of manufacturers contributed to the influenza vaccine shortages encountered in recent years. In 1980, 17 vaccine manufacturers were licensed in the United States; in 2002 the number was 5. Table 2 shows the decline in the number of vaccine manufacturers. In 2004, only four commercial companies produced childhood vaccines, and vaccines against seven childhood vaccine-preventable diseases have a single manufacturer (Orenstein, Douglas, Rodewald, & Hinman, 2005; Giffin, Stratton, & Chalk, 2004).

Table 2. Major U.S. Vaccine Manufacturers in 1980 and 2002

Major U.S. Vaccine Manufacturers in 1980		Major U.S. Vaccine Manufacturers in 2002
• Merck, Sharp, & Dohme	• American Cyanamid	• Merck & Co., Inc.
• Pasteur Vaccines	• Praxis	• Sanofi Pasteur[a]
• Merieux Institute	• Parke-David	• GlaxoSmithKline (GSK)
• Connaught	• Chiron	• Wyeth-Ayerst
• Armomd Frappe	• Behring	• Chiron
• SmithKline	• Biocine	
• SSW	• Novartis	
• Human Vaccine Institute	• Wellcome	
• Wyeth-Ayerst		

[a] In 2004, Sanofi merged with Aventis Pasteur to create the Sanofi Aventis Group. The vaccine division of the Sanofi Aventis Group changed its name to Sanofi Pasteur.

Source: Shaw, 2004

4.2.2 Current State of the Influenza Vaccine Market

Nearly all of the influenza vaccine in the world is produced in nine countries.[2] In 2003, these nine countries had 12 percent of the world's population but produced more than 95 percent of the world's influenza vaccine. Of all the influenza vaccine produced in 2000, nearly 70 percent was distributed to Canada, the United States, Western Europe, Australia, and Asian countries—most notably Japan and Korea. In 2003, the proportion was nearly the same (71 percent) (Fedson, 2005b).

This globalism is reflected in the nationalities of the manufacturers and locations where the vaccines are actually produced. Table 3 shows that vaccines approved for the U.S. market during the 2005–2006 influenza season were made in three different nations by companies based in three different nations. No currently licensed, inactivated influenza vaccine is produced by a U.S.-based manufacturer in a U.S.-based production facility. Although this arrangement is not problematic during annual influenza vaccine production, some are concerned that in a case of pandemic influenza, any effective vaccine(s) would be nationalized. In such a situation, vaccine would likely remain in the nation of its manufacture.

Table 3. Influenza Vaccine Production

Influenza Vaccine Product Name (Manufacturer)	Nation in Which Manufacturer is Based	Nation in Which Product is Produced	Number of Doses Produced (as estimated for 2005–2006)
Fluarix (GSK)	United Kingdom	Germany	8M
Fluvirin (Chiron)	United States	United Kingdom	18 to 26M
FluZone (Sanofi Pasteur)	France	United States	60M
FluMist[a] (MedImmune)	United States	United States	3M

[a]LAIV

Due to a number of factors described more thoroughly in the companion brief *Influenza Vaccine Economics*, as of the 2004–2005 influenza season, three manufacturers were licensed in the United States: Sanofi Pasteur,[3] Chiron, and MedImmune (Knight, 2004). As seen in Table 4, the number of influenza manufacturers has declined due to mergers, acquisitions, and exit from the market altogether. A limited number of vaccine manufacturers creates a vulnerable influenza

[2] The nine countries that produce 95 percent of the world's influenza vaccine are Australia, Canada, France, Germany, Italy, Japan, the Netherlands, the United Kingdom, and the United States.

[3] In 2004, Sanofi merged with Aventis Pasteur to create the Sanofi Aventis Group. The vaccine division of the Sanofi Aventis Group changed its name to Sanofi Pasteur.

Table 4. Influenza Vaccines, Manufacturers, and Seasons during which each Vaccine Was Sold

Vaccine Trade Name	Manufacturer	Influenza Season[a,b]												
		1993–94	1994–95	1995–96	1996–97	1997–98	1998–99	1999–00	2000–01	2001–02	2002–03	2003–04	2004–05	2005–06
Fluarix	GlaxoSmithKline (GSK)													●
FluMist[c]	MedImmune Vaccines, Inc.											●	●	●
Fluogen	Parkedale Pharmaceuticals Inc.[d]						●							
	Parke-Davis	●	●	●	●									
FluShield[e]	Wyeth Laboratories, Inc.	●	●	●	●	●	●	●	●	●	●	●		
Fluvirin[f]	Chiron Corporation												[g]	●
	Evans Vaccines Ltd.											●		
	PowderJect Pharmaceuticals plc									●	●			
	Medeva Pharma Ltd.		●	●	●	●	●	●	●					
Fluzone	Sanofi Pasteur Inc.[h]								●	●	●	●	●	●
	Connaught Laboratories	●	●	●	●	●	●	●						
Flu-Imune	Lederle Laboratories	●												

[a] Vaccine Adverse Event Reporting System (VAERS) data used in this table include manufacturer and trade name information taken only from specific incidence reports of vaccine adverse reactions. Data that did not specify specific influenza seasons were not used.

[b] Influenza seasons 1993–1994 through 2000–2001 (CDC, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000). Influenza seasons 2001–2002 through 2004–2005 (FDA, 2005b).

[c] Wyeth and MedImmune had a collaboration for the commercialization of FluMist for the 2003–2004 influenza season. The companies announced the dissolution of their collaboration in April 2004.

[d] Parkedale Phamaceuticals, Inc., was ordered to discontinue production of influenza vaccine following a 2000 FDA inspection.

[e] 1993–1994 trade name not available. Wyeth left the market after losing $50 million over the prior three influenza seasons; 2001–2002 was the worst season, during which the company lost $30 million and had 7 million doses of the vaccine that never sold (Ferguson, 2004).

[f] In 2003, Chiron acquired PowderJect as a wholly owned subsidiary. In 2001, PowderJect acquired Medeva—which had previously acquired Evans Medical Ltd.—and restored the Evans name to Evans Vaccines Ltd., a wholly owned subsidiary of PowderJect. Prior to this, Evans Medical Ltd. had acquired the vaccine business of Wellcome. For more information on company acquisitions and mergers, see *Vaccine Identification Standards Initiative: Manufacturer Abbreviations* (CDC, 2003).

[g] On October 5, 2004, Chiron's influenza vaccine plant was forced to cease production by government regulators due to contamination issues.

[h] In 1999, Aventis Pasteur, Inc., obtained FluZone vaccine ownership from Connaught Laboratories, Inc. In 2004, Sanofi merged with Aventis Pasteur to create the Sanofi Aventis Group. The vaccine division of the Sanofi Aventis Group changed its name to Sanofi Pasteur.

vaccine supply chain (National Vaccine Advisory Committee, 2003; Danzon, Periera, & Tejwani, 2005).

The 2004–2005 influenza vaccine shortage proved to be a recent example of the detrimental effects that may result within an industry with such a small number of suppliers. In October 2004, Chiron's Liverpool, England, factory, which sold 90 percent of its vaccine to the United States, was shut down by U.K. regulators for contamination of its vaccine. Closure of the factory reduced the vaccine supply by 48 million doses, approximately half of the anticipated supply needed for the 2004–2005 influenza season.[4] By the time the contamination was discovered, it was too late to increase production at other facilities (Danzon et al., 2005; DesRoches, Blendon, & Benson, 2005; Enserink, 2004).

Even in less dramatic circumstances, delays in vaccine distribution can also create problems. In the 2000–2001 influenza season, production problems resulted in shipment delays. This created a de facto shortage of influenza vaccine (U.S. General Accounting Office, 2001; Layton, Honeycutt, Levy, Kessler, & Liao, 2001).

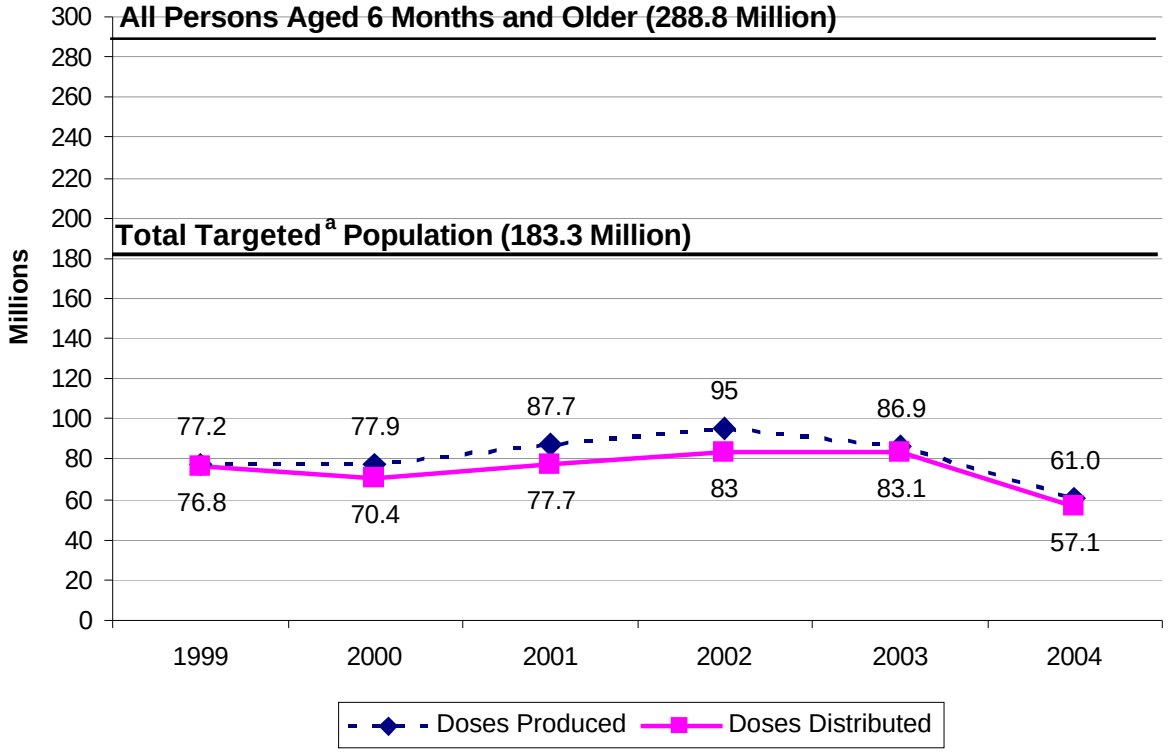
The most doses ever produced for the United States was 95 million in 2002. Nevertheless, 183.3 million doses would be needed to provide vaccine to all the groups recommended by the Advisory Committee on Immunization Practices (ACIP). Figure 5 illustrates the number of doses manufactured and distributed between 1999 and 2004 (CDC, 2005b).

4.2.3 Nature of the Influenza Vaccine Market

When asked about the most predictable element of the influenza vaccine market from year to year, one manufacturer responded by saying, "The predictable part of it is that we know it's always going to be different." As with other vaccines, the number of influenza vaccine manufacturers has dwindled in recent years, down to three manufacturers in the 2004–2005 influenza season. Given that one manufacturer (Chiron) was forced to cease production during that season, only two manufacturers (Sanofi Pasteur and MedImmune) supplied vaccine. Only one of the two (Sanofi Pasteur) had a vaccine that was approved for administration to all age groups. In the 2005–2006 influenza season, CDC predicts that there will be four licensed manufacturers. In addition to Chiron's anticipated return to the U.S. market, in late August 2005,

[4] Although the overall vaccine supply was cut nearly in half, Chiron's vaccine was not approved for use in children less than 4 years of age. Because all of the vaccine approved by the FDA for administration to children 6 to 23 months of age (the newly defined ACIP target group) was made by Sanofi Pasteur, no actual shortage of influenza vaccine occurred for the 6 million children in this group.

Figure 5. Influenza Vaccine Doses Produced and Distributed for the U.S. Market 1999–2004



[a]Targeted population includes those 65 years of age or older, children 6 to 23 months of age, and those 2 to 64 years of age with chronic illnesses.

Sources: CDC, 2005c; Santoli, 2005.

GlaxoSmithKline (GSK) received FDA approval to enter the U.S. vaccine market (CDC, 2005d; FDA, 2005a).

Compared to other product lines that vaccines may compete against within a company, low profit margins and high financial risk often cause vaccines to appear unattractive (Knight, 2004; NVAC, 2003). Consequently, costs associated with innovation may not be worthwhile unless they can be recouped in sales over several years (Danzon et al., 2005). Interviews with manufacturers revealed that a commitment to public health and the societal value of vaccines serve as fundamental reasons for remaining in the business.

See the companion brief, *Influenza Vaccine Economics*, for a detailed analysis of the influenza vaccine market.

5. Manufacturer Decision Making

5.1 Quantity Produced

A common theme noted in the majority of interviews conducted with manufacturers was the notion of unpredictable demand as the principal bottleneck in vaccine supply. Influenza vaccine production has increased substantially since the mid-1980s, a period in which roughly 20 million doses were distributed annually. This increase may be attributed in part to Medicare Part B coverage of the vaccine and its administration beginning in 1993. However, although influenza vaccination rates have increased, they remain unpredictable because less than 50 percent of the recommended population is vaccinated (Danzon et al., 2005).

Interviewed manufacturers stated that they could provide sufficient supply if given a clear indication of the level of demand with adequate advance notice. Given the inability to use influenza vaccines for more than one season, manufacturers are hesitant to produce more vaccine than they predict can be sold in a given season.

Calculating exact demand (how much can be sold) for influenza vaccine is more challenging than calculating demand for childhood vaccines because the groups for whom influenza vaccine is recommended do vary somewhat from year to year. As such, is it difficult to calculate a specific cohort to whom the vaccine will be administered, as one expert explained,

> *… we don't have other signals in society that tell us what the size of the market is going to be. We have that for all of the pediatric vaccines simply because demographers can tell us what the birth cohort is going to be every year so we know 5 years from now how many babies are going to be born … and [we] multiply it by 3 and know the number of doses of vaccine you're going to have to give for a primary series … We don't have that kind of signal for the demand of flu vaccine.*

A vaccine manufacturer commented,

> *[we] … go by the seat of our pants. The vaccine companies have to look at how much they sold last year …. They sort of eyeball that number and they take a guess. They say, "Let's increase it by 5%." Then somebody says, "Lets be cautious. We might get stuck. This is not our most interesting product anyway. Let's just increase it by 3%." So they make very conservative assumptions about the growth of the market.*

Another manufacturer explained that it tried to balance an interest in promoting public health while making pragmatic business decisions, stating,

Clearly, our organization is extremely public health oriented. At the same time, it's a business, and you're not going to see GM make 5 million Cadillac Escalades when there's no demand for them. So it's kind of odd that the government would expect all those years for us to continue to throw millions of doses of vaccine away every year and not eventually take a hit on it.

Because vaccine manufacturers do not want to make more vaccine than they anticipate they can sell in a given influenza season, they rely on what is known as prebooking. Prebooking is used by purchasers and providers to, in essence, "reserve" influenza vaccine months before the influenza season. A more complete explanation of prebooking and other issues related to purchase and distribution of influenza vaccine is in the companion brief *Influenza Vaccine: Who Buys It and Who Sells It.* One manufacturer explained, "This year we delayed prebooking to determine whether others would be in the market. We delayed as long as we could until April and completed prebooking in May."

5.2 Investment in New Technologies

Given the challenges apparent in the current, egg-based approach to influenza vaccine production, scientists are investigating a variety of ways to improve the means by which influenza vaccines are produced and administered, including updated techniques for vaccine production such as mammalian cell culture techniques and reverse genetics.

5.2.1 Cell Culture

During the 2004–2005 influenza season, many media reports mentioned cell culture as a means of overcoming the shortcomings of egg-based production. Vaccines have been produced using cell cultures since the 1950s. Vaccines for polio, measles, mumps, and rubella are all examples of cell-cultured vaccines. In the mid-1990s, researchers started to report using cell culture to produce influenza vaccines (GSK, 2005). Some of the reported benefits of this technology include equivalent or better efficacy with lower contamination risk, more controlled setting, less waste, and ability to provide surge capacity by restarting production within a season should problems arise (Tree, Richardson, Fooks, Clegg, & Looby, 2001; Lister, 2004; Rosenwald, 2004). An additional advantage is that cell culture may be more reliable when viruses will not grow well in egg culture. In fact, some viruses can kill the eggs, halting viral growth (and therefore vaccine production in those eggs). This problem would potentially be significant in case of an avian influenza strain. Key informants and others caution that although the technique may enable the virus to grow more uniformly and predictably, it may not significantly enhance the turnaround time for producing the vaccine (Brown, 2004).

Furthermore, there are challenges to producing yields in sufficient amounts, and some are concerned about the possibility of introducing unknown contaminants, so-called "advantageous agents" from mammalian cell lines. One example of advantageous agents contaminating vaccine is seen in the discovery of SV40 in polio vaccine in the late 1950s and early 1960s.[5]

5.2.2 Reverse Genetics

Another promising technique in the FDA approval process is reverse genetics (RG). A trial-and-error process is currently used to obtain virus strains with the proper characteristics needed for vaccine production. The RG process clones and combines the desired parts of the viral genome to create virus strains with the correct combinations of traits to stimulate immunity and promote growth in eggs (Lister, 2004). One advantage of RG is that the process for preparing reference virus strains can take as little as 15 to 20 days (instead of the many weeks needed for the current genetic reassortment approach) (Fedson, 2005a, p. 192). The techniques necessary for RG are associated with patents. At least two academic institutions and one pharmaceutical company (MedImmune) hold the intellectual property (IP) rights for RG. Although MedImmune has agreed to permit use of its RG technology to produce reference virus strains for research or for public health purposes, all patent holders require royalty payment for RG-developed reference strains used for commercial development. As a result, the additional cost associated with royalty payments makes it unlikely that commercially developed, RG-engineered influenza vaccines would be sufficiently profitable to make them appealing for development (Fedson, 2005a). Nevertheless, in case of a public health emergency, it appears likely that these issues would not prohibit development of vaccines—albeit as a response to rather than prevention of a public health threat.

The advantages and disadvantages of cell culture and reverse genetics are summarized in Table 5.

*5.2.3 **Intranasal Vaccines***

The FDA approved an LAIV for intranasal administration in 2002. Although not a new vaccine technology, per se, the fact that it uses a new approach (live attenuated) to stimulating an immune response and a new means of administration (intranasal) makes it worthy of mention.

[5] Between 1955 and 1963, U.S. polio vaccine was produced with cell culture techniques using cells from monkeys. In the early 1960s, researchers discovered a virus found in monkeys (SV40) in some polio vaccines. Subsequently, SV40 was found in some human cancers (Stratton, Almario, & McCormack, 2002). Although scientific evidence—including an examination by the Institute of Medicine—does not support the assertion that contaminated polio vaccine has caused cancers in humans, the incident does illustrate the point that cell culture-based vaccines are not without risks.

Table 5. Advantages and Disadvantages of Cell Culture and Reverse Genetics

	Advantages	Disadvantages	Comments
Cell Culture	Process may be several weeks to few months faster Useful in the case of avian influenza	Achieving sufficient yield remains a significant challenge Requires initial research investment Potential for mammalian cell contamination	The U.S. government has provided funding to support cell-culture vaccine development for influenza
Reverse Genetics	Process may take as little as a few weeks	Proprietary technique No history of commercialization	

Intranasal vaccines stimulate the local immune system of the upper respiratory tract, whereas injected vaccines stimulate a systemic immune response characterized by appreciable levels of antibodies to influenza virus surface proteins circulating in the blood (Cox, Brokstad, & Ogra, 2004). Influenza vaccines administered intranasally stimulate a longer-lasting and broader range of immune responses compared to the injected, inactivated influenza vaccines (Belshe et al., 2000; Gaglani et al., 2004; Halloran et al., 2003; Nichol et al., 1999), but have not stimulated high levels of circulating antibodies (Gaglani et al., 2004). LAIV administered intranasally offers some practical advantages for administration such as averting the need for needle disposal and storage—on the other hand, its current formulation, which must be stored frozen, offers some practical disadvantages.[6] An additional disadvantage, compared to inactivated influenza vaccine, is that LAIV is more costly (about twice the price). Additional research on the immune system may lead to the identification of new approaches for fighting infections and selecting potential antigens more effectively and precisely (Landry & Heilman, 2005).

While an increased interest in the development of alternatives to needle administration of vaccines has resulted in promising new discoveries in recent years, slim profit margins (when compared to other pharmaceutical "blockbusters"), fixed market size, and a relatively long research and development period caused many companies to lean toward producing more profitable drugs that people take daily, instead of vaccines that are administered once a year (NVAC, 2003; Rosenwald, 2004).

[6] MedImmune is developing a second-generation intranasal vaccine that will not require frozen storage. It is anticipated that this formulation will be available during the 2007–2008 influenza season.

5.2.4 Other Approaches

Other options for future vaccine development include an influenza vaccine with cross-antigen protection that would not require annual revaccination and influenza vaccines made with subunit or DNA viruses (Girard, Cherian, Pervikov, & Kieny, 2005).

5.3 Entry Into and Exit from the U.S. Influenza Vaccine Market

The opportunities and barriers to entry into and exit from the U.S. influenza vaccine marketplace exist within a broader context of the pharmaceutical industry. Whereas vaccine companies were once independent business entities, over the years through mergers and acquisitions (see Section 4.2) vaccine production has become the business of small units within larger pharmaceutical companies. The decision of a pharmaceutical company to enter into or exit from a given economic market is based largely on economic motivators. "The drugs most coveted by pharmaceutical companies are … those taken every day for life, such as the ones for lowering cholesterol or keeping blood pressure in check" (Lax, 2004, p. 262). With the knowledge that profit is a significant motivator, it is easier to understand vaccine manufacturers' desires to cushion the potential financial risks unique to the influenza vaccine market. As such, one would anticipate that manufacturers would be eager to obtain outside support for research and development activities.

5.3.1 Opportunities

Many manufacturers indicate that government incentives in the form of grants, tax incentives, education programs, guaranteed market and price, and government buy-back programs are needed to bolster the fragility of the current influenza vaccine system (NVAC, 2003; Knight, 2004). Some manufacturers feel that tax credits to offset costs of clinical trials or facility renovation/construction may encourage new manufacturers to enter the market. One manufacturer stated,

> *… You need to ensure that there are more people in the market who can obtain licensure and more modern production capabilities. HHS is making clear steps to do this. They [NIH] just let out two large RFPs [to support development of cell culture-based influenza vaccines], which we've applied for which essentially give companies a free ride because they pay for all the development costs and costs associated with obtaining licensure.*

Creation of a government surplus purchase program is one means of shifting some of the risk of overproduction from the manufacturer to the government. Manufacturers may be more inclined to increase the amount of overproduction if the government devised a system to purchase unused surplus at the end of the influenza season (Lister, 2004).

Without such incentives, many potential market entrants lack the capital to proceed with the lengthy and costly process of bringing a product to market. One manufacturer reported,

> *It's very difficult for new entrants like us to enter the market without incentives. We've been working on this the last 3 years, but we've been limited because we don't have the money to move this forward. You see, Wall Street doesn't see the immediate return on this type of investment.*

Another explained that public agencies can support the vaccine industry by increasing demand for influenza vaccine through public education campaigns and provider reimbursement:

> *The government can help us by ensuring that the market grows by doing things like educating and providing appropriate reimbursement. If the government can play that significant role and ensure that more people get immunized through these types of efforts, you're going to see that manufacturers are going to invest, compete, and reinvest, and realize that it's going to remain profitable and worthwhile to continue to grow their business.*

In 2003, FDA established a committee to investigate options for working with overseas governments to harmonize regulations for vaccine approval. Proponents feel that efforts should be made to obtain mutual recognition of lot release tests for various vaccines by harmonizing the content and format for submitting license applications in the context of the International Committee on Harmonization (NVAC, 2003). One manufacturer commented,

> *I think down the road it will make things easier if there is one general approach. My idea is that when there is harmonization, things will become easier and more manageable. Maybe it can create some flexibility in supply as well.*

5.3.2 Barriers

Given the volatile demand; high development, approval, and manufacturing costs; and the perception of low return on investment in the vaccine industry (compared to other pharmaceuticals), many manufacturers are reluctant to enhance their current production technology (Danzon et al., 2005; NVAC, 2003). "Keep in mind that influenza vaccine has always been a very cheap product, and so there never has been much incentive to modernize the technology for producing it," noted one manufacturer. Another informant stated,

> *It takes $100–150 million to bring a new product to market from scratch. If you only make $50 million in profit a year on that product, that's a tough sell to management.*

They want to know what the return on investment is, and that profit margin may not meet their qualifications.

The time, labor, and costs associated with the regulatory approval process are described as a barrier to manufacture by some. As one manufacturer described,

To guide a product through to regulatory approval is very expensive. You have to establish a vaccine safety database of 80,000, but each subject costs $2000, so that can add $160 million right there to address FDA concerns related to vaccine safety. Before a product can be brought to market, we have to test it on 40,000 to 80,000 subjects.

Moreover, slight modifications to production processes or packaging may require expensive product reviews. Frequent FDA inspections of production facilities and costs associated with facility upgrades, needed to adhere to current Good Manufacturing Processes (cGMP), increase the costs of vaccine production (Sloan, Berman, Rosenbaum, Chalk, & Giffin, 2004). Consequently, some argue that regulatory costs stifle development of better technologies for manufacturing vaccines (Knight, 2004). However, one expert in the area of vaccine manufacturer with whom we spoke clarified that it was not the costs of meeting cGMP that were a barrier but the costs associated with the necessary clinical trials for safety. Licensed vaccine manufacturers with whom we spoke would not (for proprietary reasons) provide specific answers concerning costs associated with production, so we were unable to precisely explain the costs associated with the regulatory (or other) processes.

6. Summary and Conclusion

In summary, the process by which influenza vaccine is manufactured is more complicated than that for other pharmaceutical products—even other vaccines. This is due to several reasons, most notably because, unlike other vaccines, "Flu vaccine is new every year. It's different from every other vaccine, and there are unique challenges every year. Making vaccines is not an easy process … " As another expert key informant explained, "For manufacturing the vaccine, it's not just like turning on a spigot and some chemicals come out and you can stamp out some pills. These are living organisms that sometimes behave differently. It's very complex to manufacture biologics."

Key informants recommended that our analysis and reporting of the influenza vaccine issues emphasize the complexity not only of the manufacturing process, but all other related factors as well. Such factors include economic issues—"From everything you hear and see, there's not as much profit as with other pharmaceuticals. There's a lot more [financial] risk with

vaccines. … There's a lot more oversight and review (rightfully so for biologics) by the FDA." Another explained,

> *We are a for-profit, publicly traded company. What I like to tell people is that neither Santa Claus nor UNICEF is listed on the NYSE. If you have a money-losing product and there are others making it, it's time to kiss it goodbye.*

Some of the economic risk that manufacturers face could be reduced by some means of financial support.

> *… to ensure adequate vaccine supply, the government needs to share the risk or at least the consideration of some kind of buy-back mechanism. Negotiate in the early part of the season how many doses the manufacturers will produce, which, if left unsold at the end of the season, the government would purchase at some predetermined price.*

In addition, there is the complicated relationship between influenza vaccine supply and demand. As explained more thoroughly in the companion brief *Influenza Vaccine Demand: The Chicken and the Egg*, demand appears to be the tail that wags the dog as far as supply is concerned. If demand for vaccine is sufficient, manufacturers will meet the demand with sufficient supply. One of the ways to increase demand was mentioned in several interviews.

> *Recommendations drive demand, and demand drives supply, it's that simple. If there are strong, clear recommendations for who should get flu vaccine in place, then the demand will be there, and if the demand is there, we'll ramp up and meet that demand with adequate supply.*

Many key informants noted the significance of recommendations from ACIP and/or CDC and how they act to drive vaccine demand. Although such recommendations can serve to increase demand by defining broader target groups for immunization, recommendations can also be part of a larger campaign of public information.

> *I really think that there needs to be a lot more education. The government can play a much larger role in educating the public of the importance of the influenza immunization and the importance of the disease. One great example of how effective a role the government can play in terms of leadership is last year … they had Julie Gerberding on the public service announcements, in front of the press, and [at] meetings … making sure the priority groups got immunized first in the case of a shortage. I think that was*

relatively successful. I think it was pretty effective because we had CDC getting out in front, telling people what they should be doing.

There were also those who thought that the ideal is a so-called "universal recommendation." "The only way of leveling this thing out so that it's a workable situation is to have a consistent, perhaps universal recommendation so that you know you will have this every year," one key informant contended.

Immunization tops the list of the 10 great public health achievements during the last century (CDC, 1999). Despite this achievement, due to a variety of factors, each year less than half of those who are at highest risk for influenza-related complications are vaccinated. Meanwhile, influenza is the leading cause of mortality due to infectious disease (CDC, 2005a), causing an average of 36,000 deaths (Thompson et al., 2003) and 226,000 hospitalizations annually (Thompson et al., 2004). As such, influenza vaccine manufacture is the cornerstone of reducing influenza-associated mortality.

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