



2007-2008 Influenza Vaccine Production & Distribution

MARKET BRIEF



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I. Preface

During the last influenza season, healthcare providers and patients saw a consistent and reliable flow of vaccine that began shipping early. Overall, vaccine moved efficiently through the supply chain with little to no delay.

Late-season concerns regarding the efficacy in matching some vaccine strains emerged. However, health experts report that flu vaccination, regardless of how perfectly or imperfectly strains match from season to season, still mitigates the flu and its related complications.

The following occurred during the 2007-2008 influenza season:

- **Flu Vaccine Manufacturing Increased.** The Centers for Disease Control and Prevention (CDC) estimate that 140.6 million doses of flu vaccine were ultimately produced this season after initial estimates of up to 134 million doses. This amount exceeds average production since 2000-2001, and is more than any past season including 2006-2007, which saw 120.9 million doses produced.
- **Efficient Timing and Distribution of Vaccine.** Flu vaccine manufacturing and distribution early in the flu season resulted in more than adequate supplies. The bulk of production (approximately 97%) was completed by Nov. 1, 2007 – before influenza’s typical peak in February. This enabled providers to have a reliable supply of vaccine on hand to immunize patients early and throughout the season.
- **Increased Government and Industry Focus on Utilization of Flu Vaccine.** A number of campaigns by local, state, and the federal government urged greater utilization of flu vaccine. This was evidenced by new guidelines aimed at increasing the flu vaccination rate among healthcare workers. Increased messaging by the CDC and others urged patients to utilize flu vaccine to protect themselves, loved ones, and daily contacts. There was also a significant increase in spending on direct-to-consumer (DTC) advertising that emphasized the importance of vaccination.
- **Increased Focus on Broadening the Influenza Vaccination Season.** Widespread outbreaks of flu activity in 49 states were reported in February 2008, following an initial slow start to the season. The timing of these outbreaks highlights the importance of a broadened immunization schedule that extends past traditional timeframes and continues into January, February, and beyond. Also contributing to the importance of a broadened immunization season is the need to vaccinate a growing target population (218 million Americans) against seasonal influenza.

This report by the Health Industry Distributors Association (HIDA) – the third in a series – explores the dynamics involved in influenza vaccine production and distribution. For information on past seasons or for further details on influenza production and distribution, visit www.HIDA.org or www.FluSupplyNews.com.

II. Distribution’s Role in Influenza Vaccination

The influenza vaccine supply chain is divided into two channels. In one channel, vaccine doses are sold directly by the manufacturer to a customer (a physician office, public agency, pharmacy, community vaccinator, etc.). In another channel, vaccine is sold by manufacturers to distributors, who in turn deliver vaccine to their customers – primarily physician offices [Figure 1].

During the 2007-2008 influenza season:

- Manufacturers shipped about 50% of the flu vaccine supply directly to their customers [Figure 2].
- Distributors committed to order and deliver approximately half (the remaining 50%) of the vaccine supply – consistent with the past season.

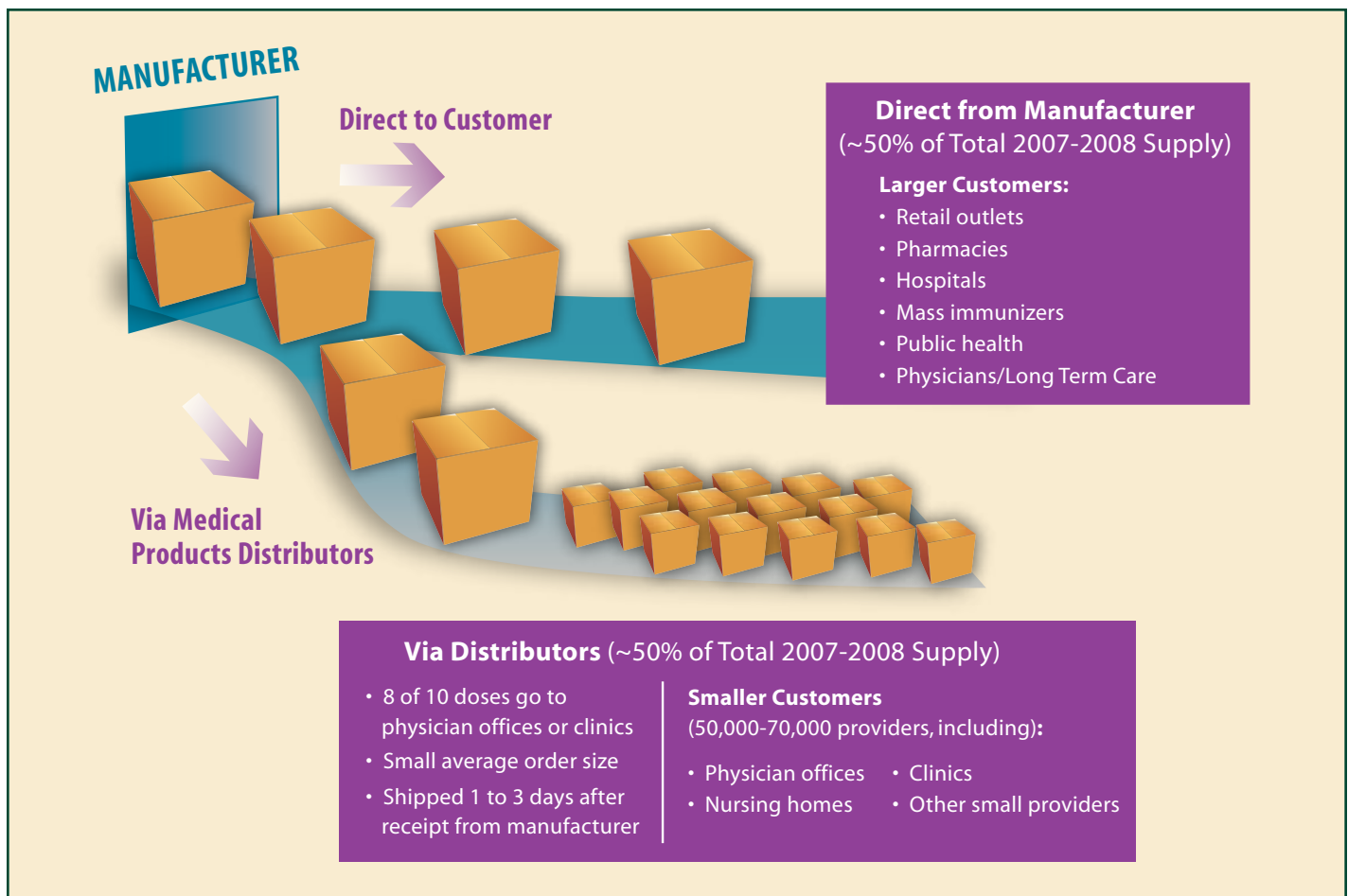
For the purposes of this report, “distribution” refers to how vaccine travels through the supply chain, that is the process of transferring vaccine to the end user. The term “distributor” refers to distributors, who deliver vaccine (along with other products and services) across healthcare settings that include physician offices, hospitals, and nursing homes. The term “distributor” may also refer to wholesalers (firms that deliver to larger providers such as government agencies, hospital pharmacies, home health facilities, and others).

Distributor Facts

- Generally, one to three days pass between the arrival of flu vaccine at a distributor’s loading dock and its delivery to the customer.
- Distributors are the primary channel for delivering influenza vaccine to physician offices, the preferred venue for vaccination.
- More than 600 distributors across the United States operate more than 800 distribution centers.
- The distribution system is designed to handle a range of delivery volumes to a wide variety of customers.
- Distributors serve more than 50,000 points of care across the country, and more than 12,000 U.S. medical practices with six or fewer physicians.¹

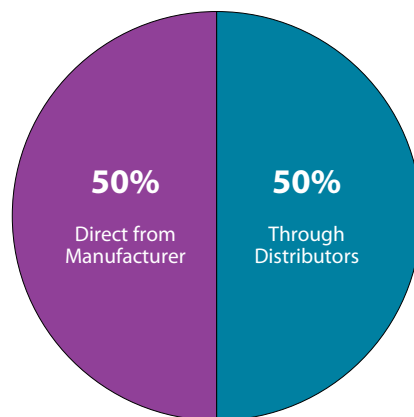
¹ HIDA 2005 Distribution Market Report; HIDA 2006 Physician Market Report.

Figure 1: Two Ways Vaccine Gets to Market



Source: HIDA research, industry sources

Figure 2: Percentage of Vaccine Sold by Channel in 2007–2008



Source: HIDA research

III. Past, Current, and Potential Influenza Vaccine Production for the U.S. Market

Five manufacturers (CSL, GlaxoSmithKline, MedImmune, Novartis, and sanofi pasteur) produced seasonal influenza vaccine for the U.S. market during the 2007-2008 season. The largest share of production, approximately 37% of doses, was produced by sanofi pasteur [Figure 3]. CSL entered the market in 2007, with a planned total production of 2 million doses.

A number of manufacturers are currently exploring ways to produce influenza vaccine using cell-based technologies. These new production methods do not require the use of chicken eggs to incubate the vaccine. The U.S. Department of Health and Human Services (HHS) has issued more than \$1 billion in grants to GlaxoSmithKline, MedImmune, Novartis, sanofi aventis, DynPort, and Solvay to explore these new production methods². Novavax, Inc. has also announced plans to begin clinical trials of a new cell-based vaccine³. While these production methods are promising, they have not begun to produce vaccine for the U.S. market.

For the 2007-2008 season, approximately 140.6 million doses were actually produced—the largest volume to date. The total approximate number of doses distributed⁴ was estimated to be 112.8 million doses [Figure 4].

Approximately 27.8 million doses were not distributed. The number of “distributed doses” (those ordered by or sent to a distributor or provider) does not necessarily reflect the number of doses administered to or demanded by patients.

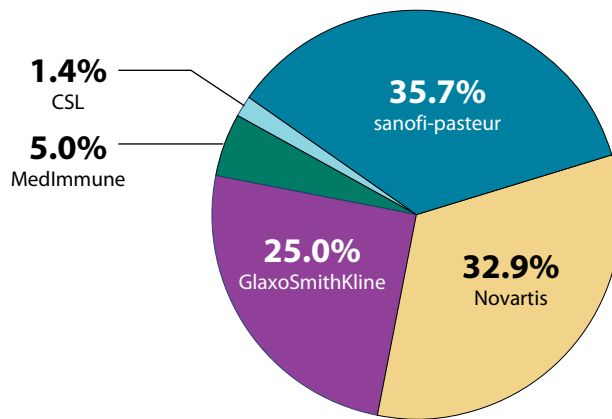
Note: Total production capacity from season to season may vary depending on the entry of new suppliers into the market, the development of new manufacturing technologies (e.g., reverse genetics, cell-based, etc.), the construction of new facilities that increase the supply capacity of current producers, and the yield of seed lots.

² “HHS Awards Contracts Totaling More than \$1 Billion to Develop Cell-Based Influenza Vaccine.” U.S. Department of Health and Human Services (May 4, 2006).

³ “Novavax Opens Its First U.S. Vaccine Plant” (May 1, 2008).

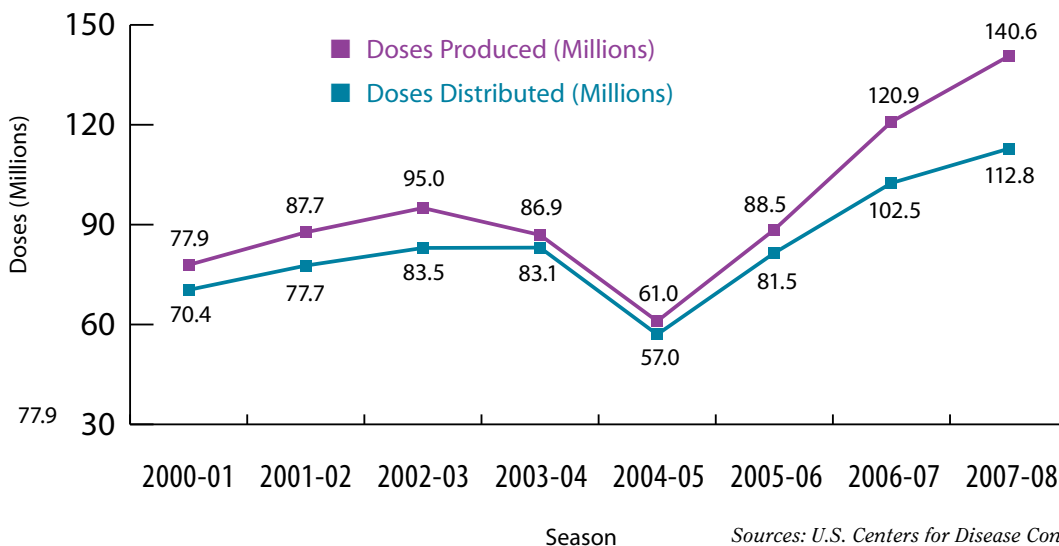
⁴ Total distributed doses are tracked from September 2007 to January 2008 by the CDC.

Figure 3: Doses Produced in 2007-2008 (140 Million)



Source: Company press releases, Centers for Disease Control and Prevention

Figure 4: Influenza Vaccine Production for the U.S. Market, (2000-2001 through 2007-2008)



Sources: U.S. Centers for Disease Control and Prevention

In total, an average of 94.8 million seasonal flu vaccine doses have been produced for the United States each year since 2000 [Figure 4].

The global market for influenza vaccine is expected to grow by more than 13% annually through 2012. By 2012, worldwide sales are expected to exceed \$4 billion⁵.

By 2011, global demand for seasonal influenza vaccine could be as large as 600 million doses, a 50% increase from 2006 demand⁶ and a reflection of expanding vaccination guidelines to include a broader segment of the population.

During 2007, the major manufacturers reported increased or decreased influenza vaccine revenues compared to 2006 depending on the timing of vaccine sales [Figure 5]. Some manufacturers sold more

⁵ Mitchell, Steve. "Analysis: Vaccine Market to Top \$23B." *United Press International* (Feb. 9, 2007).

⁶ Reinhardt, Joerg. "Vaccines and Diagnostics—A New Strategic Growth Platform." *Novartis Vaccines and Diagnostics* (Jan. 18, 2007).

vaccine in the second and third quarters. This was because the selected vaccine strains could be grown, and made into finished vaccine, more quickly in 2007 than in 2006.

Figure 5: Change in Fourth Quarter Influenza Vaccine Revenues, 2006-2007

Manufacturer	Increase in Influenza Vaccine Revenue (Percent)
Novartis	"Weak" fourth quarter sales
sanofi pasteur	-2.40%
GlaxoSmithKline	62%
MedImmune	194%

Source: Company press releases and financial reports

IV. Preferred Sites for Vaccination

Across all age groups, patients prefer to receive influenza vaccinations at a doctor's office [Figure 6]. Depending on age group, between 39% and 46% of patients actually receive their influenza vaccine in a physician office. For patients between the ages of 18 and 65, the workplace is also a popular vaccination site.

Figure 6: Sites for Flu Vaccination: Actual vs. Preferred

		18-49	50-64	65+
Doctor's office	Actual	46%	39%	45%
	Preferred	59%	46%	52%
Workplace	Actual	26%	18%	1%
	Preferred	25%	17%	0%
Clinic/community health center	Actual	4%	16%	18%
	Preferred	2%	13%	14%
Retail Store	Actual	10%	6%	11%
	Preferred	0%	2%	5%

Source: Centers for Disease Control and Prevention/Gallup Organization, courtesy of the American Academy of Family Physicians (2005-2006)

V. Managing Influenza with Diagnostic Resources

A recent CDC survey found that 36% of family practitioners and pediatricians order rapid diagnostic flu tests⁷. These tests can mitigate the spread of influenza by helping clinicians ensure timely and appropriate treatment for patients who exhibit influenza-like-illness (ILI) symptoms. Diagnostic testing is becoming more prevalent as influenza can be difficult to diagnose correctly due to similar symptoms found in other upper respiratory infections, according to some research. A New England Journal of Medicine study found that, in the outpatient setting, 83% of laboratory-confirmed cases of influenza were misdiagnosed in patients younger than age 5⁸. To date, the fastest diagnostic tests can be run in about 10 minutes and have a sensitivity of 94% for Influenza type A with a nasal swab sample.

⁷ CDC MMWR Jan. 25, 2008.

⁸ The Underrecognized Burden of Influenza in Young Children, Katherine A. Poehling, M.D., M.P.H., NEJM, July 2006.

VI. U.S. Influenza Vaccine Sales by Type of Provider

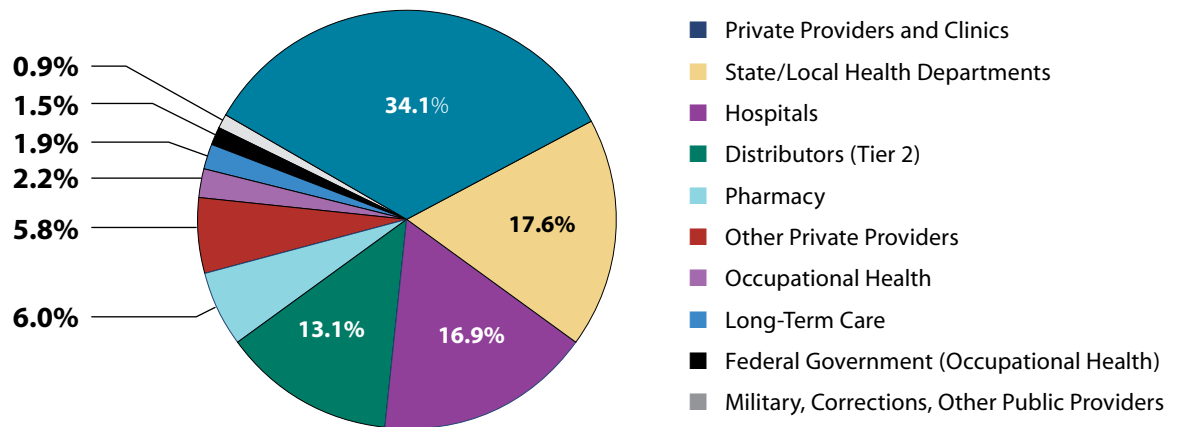
About 34% of vaccine produced (including that sold directly and through distributors) was sold to physician offices [Figure 7]. Of all doses, 17.6 % went to state and local health departments, 16.9% were sold to hospitals, and 19.1% went to pharmacies and tier two (or secondary) distributors, according to the CDC. Eight out of 10 doses sold by distributors were provided to physician offices.

The most noticeable shifts in vaccine sales by provider type occurred among hospitals, which saw an increase from 9.9% in 2006-2007 to 16.9% this season.

However, a number of factors impacted the way vaccine sales by provider type may be viewed this season, including:

- **The re-coding of provider types by the CDC.** (For example, an increase in the “other private providers” category from 2.9% last season to 5.8% this season.)
- **An increase in overall vaccine supply, with differential increased ordering among different provider types.** (For instance, groups with a known patient population and fixed ordering patterns such as the military may not have increased order volume and therefore comprised a smaller percentage of a greater number of vaccine doses.)

Figure 7: 2007-2008 U.S. Vaccine Sales by Provider Type



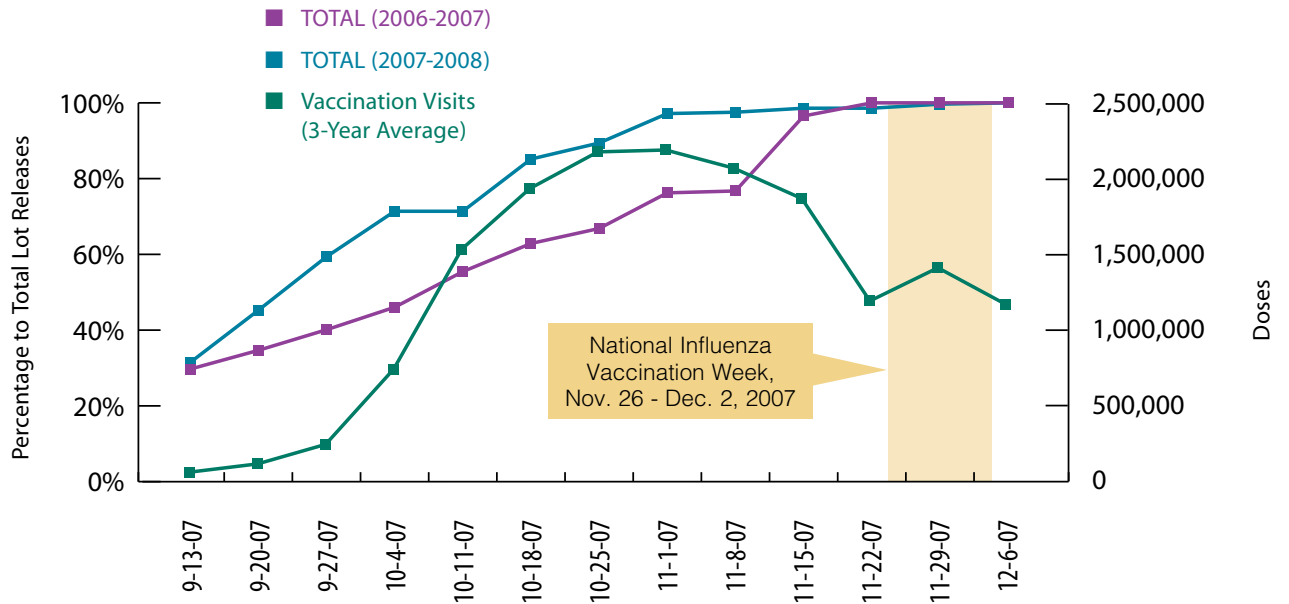
Source: Centers for Disease Control and Prevention

VII. U.S. Influenza Vaccine Demand Peaks Before Supply

Healthcare advocates increased efforts to extend the vaccination season into November and December through initiatives such as National Influenza Vaccination Week from Nov. 26 to Dec. 2, 2007. However, demand for flu shots remained at its highest levels in October and began to decline Nov. 1 when peak supply was nearly reached.

Manufacturers were able to release vaccine into the supply chain earlier in 2007 than in 2006 [Figure 8]. However, late-season outbreaks during February 2008 at colleges, universities, and other locations underscores both the length of the influenza season, and the value of vaccinating patients later in the season.

Figure 8: Cumulative Vaccine Releases, 2007-2008 Season

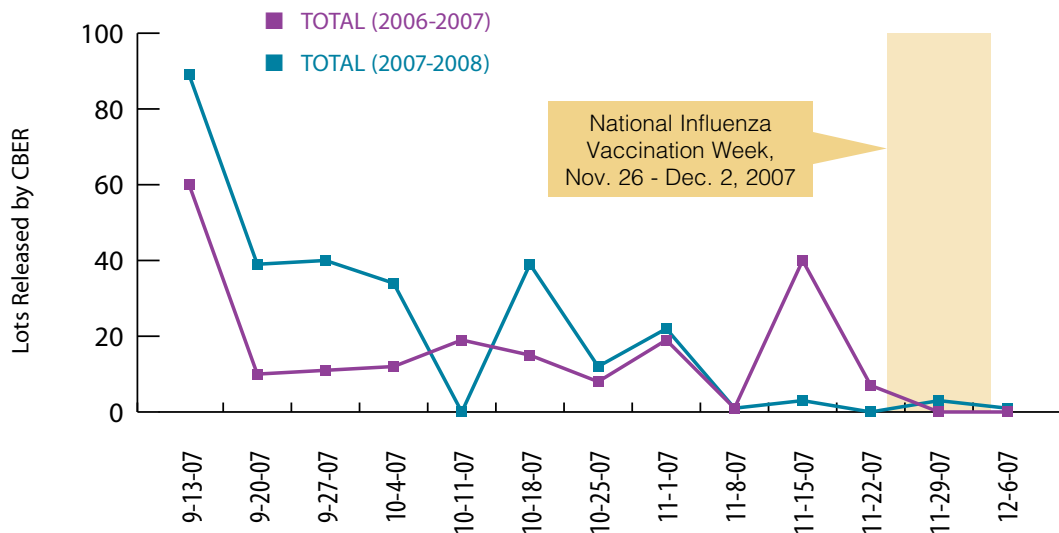


Sources: Food and Drug Administration, Center for Biologics Evaluation and Research; sanofi aventis

VIII. Number of Doses Varies Weekly

The number of doses released into the supply chain by manufacturers varies weekly, depending on the timing of production and approval processes. However, predictability of supply is important for ensuring confidence in the availability of vaccine. In 2007, more doses were available at the beginning of the season, and less volatility was experienced later in the season [Figure 9]. This helped distributors and their customers predict and plan for when they would receive, and be able to administer, vaccine.

Figure 9: Weekly Releases, 2007-2008 Season



Sources: Food and Drug Administration, Center for Biologics Evaluation and Research

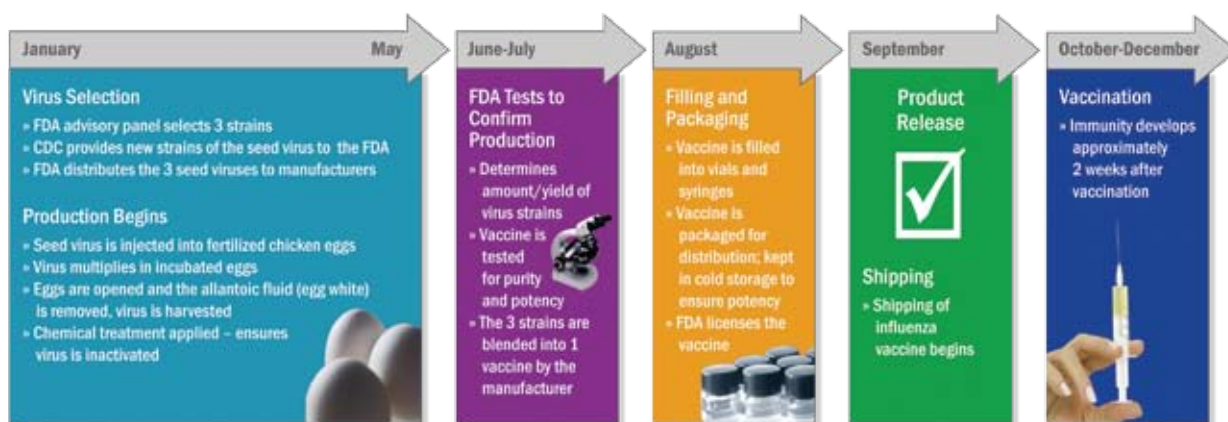
Note: The figures, timelines, and data in Figures 8 and 9 capture the FDA approval and release of already-manufactured vaccine. Approved and released vaccine has not necessarily reached physicians, hospitals, other providers, or patients—there is an inherent delay between the conclusion of the approval and release process and the delivery and administration of the vaccine.

IX. Influenza Vaccine Manufacturing Process

The manufacturing process is typically five to eight months long. It is subject to delays depending on the results of virus selection and incubation processes [Figure 10]. In 2007, manufacturers reported few difficulties in reproducing the virus, resulting in a greater number of doses supplied early in the season. However, some of the virus strains seen in the season were different than those selected for replication, meaning that vaccinated patients received a lower level of immunity.

Vaccine manufacturers are exploring new ways of producing vaccine that would be more predictable and consistent than current egg-based manufacturing. It is possible, but far from certain, that these production methods could reduce the long lead times required for current egg-based production methods.

Figure 10: Influenza Vaccine Production Timeline



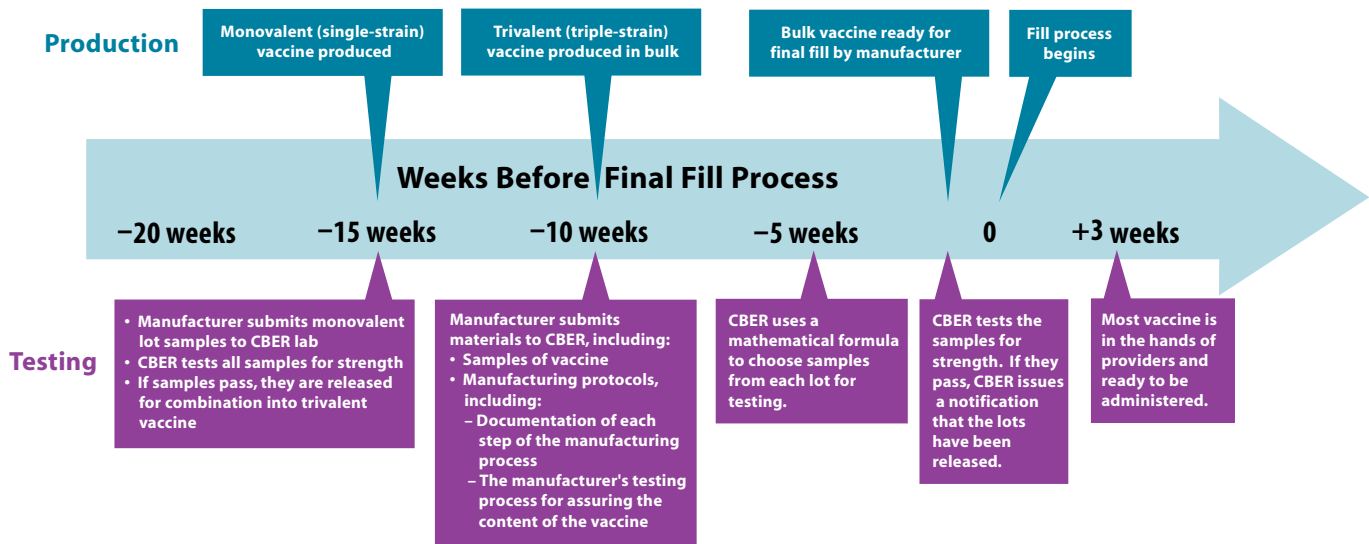
Source: www.FluSupplyNews.com

X. Lot Release Process

Manufacturers are required to submit samples of vaccine to the U.S. Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research (CBER) to ensure their safety and effectiveness. These analyses are conducted by CBER scientists at the monovalent stage (when vaccine is developed for a single strain of influenza) and at the trivalent stage (three monovalent vaccines are combined into a final vaccine against three virus strains) [Figure 11].

The lot release process must be repeated for each lot of vaccine the manufacturer produces. During the most recent influenza season, the number of lots released ranged from 12 (for CSL) to 89 (for GlaxoSmithKline). [Note: The number of doses in each lot varies by manufacturer and production facility.]

Figure 11: Influenza Vaccine Lot Release Process



Source: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research; HIDA independent research

Vaccine manufacturers are required by law to submit samples of each manufacturing lot of vaccine to CBER to ensure that they meet FDA standards for effectiveness. Once the lots are approved, they are officially released by CBER and are ready to be packaged and sold by the manufacturer. The guidelines for the lot release process appear in the Combined Federal Regulations (CFR):

• **610.1 Tests prior to release required for each lot.**

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable for such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The results of all tests performed shall be considered in determining whether or not the test results meet the test objective, except that a test result may be disregarded when it is established that the test is invalid due to causes unrelated to the product.

• **610.2 Requests for samples and protocols; official release.**

(a) *Licensed biological products regulated by CBER.* Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Biologics Evaluation and Research. Upon notification by the Director, Center for Biologics Evaluation and Research, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Center for Biologics Evaluation and Research, provided that the Director, Center for Biologics Evaluation and Research, shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

XI. Forecast for 2008-2009 Season

The outlook for the 2008-2009 influenza season is uncertain. Next year's vaccine will include three new virus strains, the first time in 20 years, and only the second time in history, that all three strains have been replaced in a single year. One of the strains, Brisbane/10, is known to be difficult to replicate. As a result, timelines for influenza vaccine production and distribution may be different than those experienced during the 2007-2008 season.

Distributors will continue to provide vaccine doses to providers as quickly as possible. However, ensuring visibility about the amount and timing of vaccine supply will be critical for avoiding misperceptions throughout the supply chain and by the public.

Planned production for the 2008-2009 season is projected to be as many as 143 to 146 million doses, about a 2% increase over 2007-2008 production [Figure 12].

Figure 12: Projected Approximate Vaccine Production, 2008-2009 Season

Company	Doses in Millions (Approximate)
sanofi pasteur	50
Novartis	40
GlaxoSmithKline	35
MedImmune	12
CSL Biotherapies	6
TOTAL	143

Source: CDC/AMA Flu Summit, 2008

Acronyms

Centers for Disease Control and Prevention (CDC)
U.S. Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Combined Federal Regulations (CFR)

Sources

- Centers for Disease Control and Prevention (www.cdc.gov)
- U.S. Food and Drug Administration, Center for Biologics Evaluation and Research (<http://www.fda.gov/cber/flu/flu.htm>)
- American Academy of Family Physicians (www.aafp.org)
- Flu Supply News (www.flusupplynews.com)

About HIDA

The Health Industry Distributors Association (HIDA) is the premier trade association representing medical products distributors. Since 1902, HIDA has provided leadership in the healthcare distribution industry.

HIDA also works closely with the manufacturing community through the HIDA Educational Foundation. This outreach

serves to build strong manufacturer/distributor relationships as well to communicate the value of distribution in the healthcare supply chain.

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