Partners in PUBLIC HEALTH

BY DENISE MYSHKO

INDUSTRY EXPERTS DISCUSS THE ROLE OF PHARMACEUTICAL COMPANIES IN PANDEMIC PREPAREDNESS.

The first influenza pandemic of the 21st century is under way. H1N1 influenza A has affected more than 207 countries and overseas territories worldwide, according the World Health Organization. As of the end of November 2009, 622,482 cases have been reported, including more than 7,820 deaths. In April 2009, the WHO declared the virus a "public health emergency of international concern" after countries around the world began reporting deaths from the combination of pig, human, and bird viruses.

In the United States, 29,348 people had been hospitalized through Nov. 30, 2009, because of H1N1, and 1,224 people have died as a result, according the Centers for Disease Control and Prevention.

Vaccines play a vital role in helping public health officials address such pandemics. In fact, public health officials need the manufacturers as much as vaccine manufacturers need government agencies.

"Since there is no commercial market for pandemic vaccines, the government has to buy them," says Daniel Adams, president and CEO of Protein Sciences.

Experts say there is an even bigger role for vaccine companies to help address public health needs.

"Being at the table as a manufacturer and provider of vaccines, particularly in the case of pandemics, is an essential part of what we believe our business model is," says Peter Lammers, VP of vaccines at GlaxoSmithKline.

"As a vaccine manufacturer, it is a core competency to continue to work with the government to address public health needs, both inside pandemic influenza and outside influenza," he continues. "GSK, as a partner in public health, aims to contribute to public health needs in ways that go beyond vaccine antigens. We are an adjuvant supplier, an antivirals supplier, and a supplier of personal protective gear. As we approach government agencies, we're approaching them as more than just a vaccine manufacturer."

> As a vaccine manufacturer, it is a core competency to continue to work with the government to address public health needs, both inside pandemic influenza and outside influenza.
>
> **PETER LAMMERS**
> GlaxoSmithKline

FAST FACT

The global H1N1 influenza vaccine market is expected to be valued at $7.03 billion by 2011, with a CAGR of 222.4% from 2009 to 2011.

MarketsandMarkets

During the H1N1 outbreak, GSK had been in discussions with WHO, the CDC, the U.S. Department of Health and Human Services, and the European Centre for Disease Prevention and Control to gain a better understanding of the new influenza A strain.

The company has been working with these authorities to help them develop estimates for manufacturing capability, timing of possible production, and to understand the benefit of using adjuvant technology in production of a potential pandemic vaccine.

In pandemic situations, there is an opportunity for companies to work with public health officials for timely development and manufacture of vaccines, says Debra Drane, senior VP of R&D at CSL Biotherapies.

"We were able to introduce a vaccine into volunteers in July and published the data in NEJM in early September, which allowed governments to make decisions very quickly," she says.

Tony Estrella, chief operating officer and co-founder of HealthiNation, says helping public health officials with pandemic preparedness can also have a positive affect on the industry's reputation.

"The pandemic H1N1 area presents an opportunity for pharmaceutical companies to enhance their credibility with the public," he says. "At the end of the day, pharmaceutical companies are offering a product that helps people. Their end goal is to positively impact health. Pharmaceutical manufacturers have to embrace the opportunity they have to be a

credible source of information for consumers."

Ms. Drane says another key opportunity for companies is to work with public health officials to educate consumers about pandemics and vaccines.

"We make flu vaccines with different strains every year," she says. "H1N1 was just another strain of the flu in terms of manufacturing a vaccine; this wasn't well-understood. The industry and government can also do a better job to educate the public on what vaccines are. People often fear what they don't understand, especially if they think it is new and different."

This strain, influenza A (H1N1), first came to the attention of doctors when an outbreak started in Mexico during April 2009. Scientists believe that the H1N1 virus mutated while in pigs into a form that affects humans.

VACCINE SAFETY

Pandemics raise concerns about the safety of vaccines. Although the CDC stressed that the H1N1 vaccines would have a similar safety profile to seasonal flu vaccines, there was concern in the media about a greater potential for side effects. One concern was the risk of Guillain-Barré syndrome (GBS), a rare disorder in which a person's own immune system damages the nerve cells. In the mid 1970s, there appeared to be a suspected link to GBS from a vaccine used for a similar swine flu.

Terri Madison, Ph.D., MPH, president of i3 Drug Safety, says regulators aimed to get the H1N1 vaccines to the market as quickly as possible through an accelerated process of review.

"Because the development process for pandemic vaccine was accelerated, the level of exposure typically seen during clinical development for a full nonaccelerated vaccine application to authorities was lower than normal," she says. "There was a smaller safety database accumulated at the time the H1N1 vaccines were authorized. Because of this smaller level of exposure from the development side, there are specific safety monitoring criteria put out by the FDA and EMEA regulators for the vaccine as soon as it hits the market."

i3 Drug Safety established an H1N1 vaccine safety surveillance program to provide access to safety information about the H1N1 vaccine safety for subjects who received H1N1 vaccines. The study, which is IRB-approved, was launched in October 2009 captures medical claims information relating to outcomes associated with H1N1 vaccine administration in near real time.

"We're using the data in a variety of ways," Dr. Madison says. "One is to inform the appropriate public health officials in the United States who monitor these types of data about what we are seeing. We also are talking with the CDC about participating in its H1N1 vaccine surveillance program."

The CDC and the FDA also jointly sponsor a national vaccine safety surveillance program, Vaccine Adverse Event Reporting System (VAERS). VAERS was established in 1990 in response to the National Childhood Vaccine Injury Act of 1986, which requires health professionals and vaccine manufacturers to report adverse events that occur after the administration of routinely recommended vaccines.

As of Nov. 20, 2009, VAERS had received 3,182 adverse event reports related to H1N1 vaccination. The vast majority (94%) of adverse events have not been serious (e.g., they encompass things like soreness at the vaccine injection site.) Of the reports, 177 (6%) involved what would be considered serious health events (defined as life threatening or resulting in death, major disability, abnormal conditions at birth, hospitalization, or extension of an existing hospitalization). The percentage of reports involving what would be considered serious health events is not different between 2009 H1N1 and seasonal influenza vaccines.

VAERS has received 10 reports of Guillain-Barré syndrome (GBS), for which follow-up assessments are under way. In the United States, about 80 to 160 cases of GBS are expected to occur each week, regardless of vaccination.

THE NEWER VACCINES

Researchers at several companies, including Baxter International, GlaxoSmithKline, Novartis, and Protein Sciences, among others, are pursuing new avenues for producing influenza vaccines. One promising avenue involves culturing the virus in cells instead of eggs. While egg-based influenza vaccines are well-proven for cost-effective production of influenza vaccine, this method lacks the flexibility to effectively address pandemics. Cell-culture based systems

20TH CENTURY FLU PANDEMICS

1918. **Spanish flu** was an H1N1 virus and affected about 40% of the world's population at the end of World War I. It is estimated that more than 40 million people died worldwide.

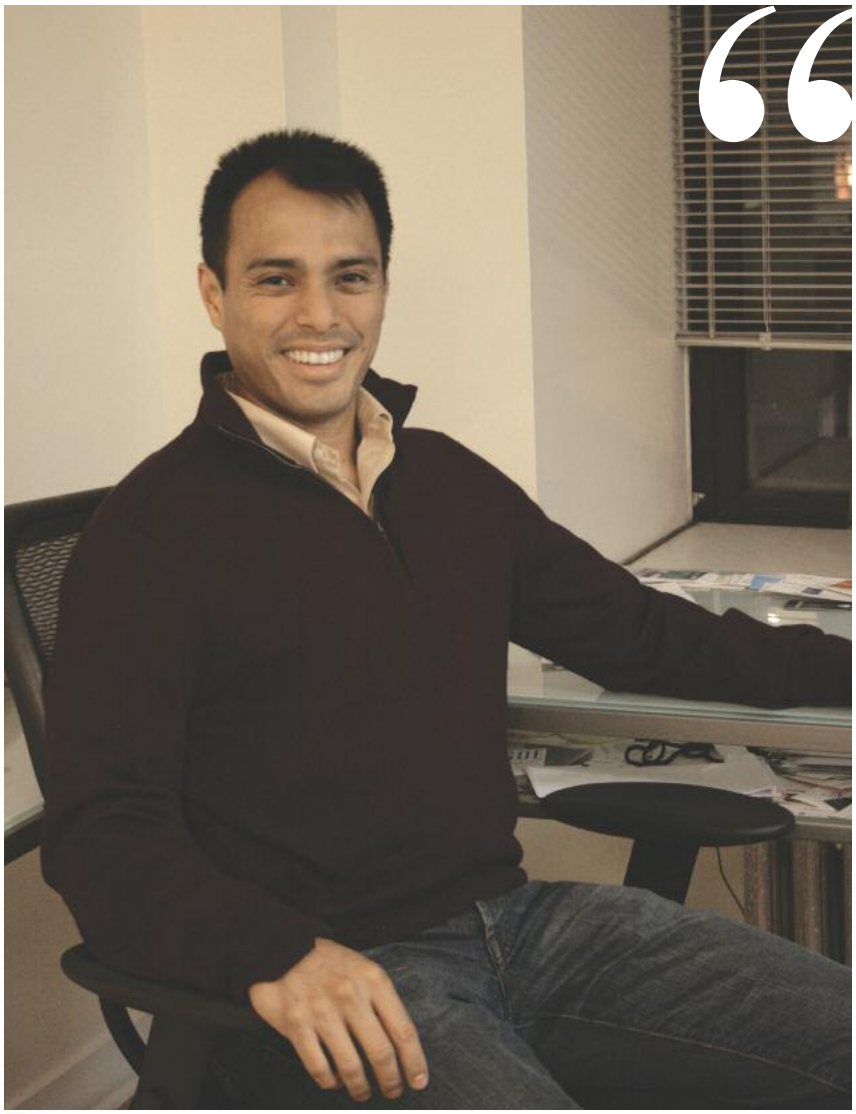
1957. **Asian flu** was an H2N2 virus. It was estimated that about 2 million people died, although the availability of a vaccine reduced the number of deaths significantly.

1968. **Hong Kong flu** was an H3N2 virus. It was estimated that about 1 million people worldwide died, mostly elderly.

Source: GlaxoSmithKline.
For more information, visit gsk.com.

Once this particular pandemic is over, pharma should take the lead in conducting an industrywide forum to share best practices for future pandemics.

DR. TERRI MADISON
i3 Drug Safety



> The pandemic H1N1 area presents an opportunity for the pharma companies to enhance their credibility. They have to embrace the opportunity they have to be a source of information for consumers.
>
> **TONY ESTRELLA**
> HealthiNation

could be rapidly expanded and scaled up when needed, although there are large up-front costs for manufacturing plants.

Most recently, Novartis in November 2009 opened a new cell culture-based manufacturing site in North Carolina. Novartis already operates a similar plant in Marburg, Germany. Total investment in the new U.S. plant was about $1 billion through a partnership between Novartis and the Department of Health and Human Services (HHS). The facility was designed to supply 150 million doses of pandemic vaccine within six months of influenza pandemic declaration.

In October 2009, Baxter International received approval in Europe for an H1N1 vaccine that is based on its proprietary Vero cell-culture technology. The company has plans to build a cell-based plant in the United States.

Mr. Lammers of GSK says its cell-based vaccine program is still in its earliest stages. The company has recently invested in a new manufacturing plant in the United States where cell-culture technology will be developed for the production of future influenza vaccines.

Protein Sciences is also pursuing a cell-based influenza vaccine through a $147 million contract with HHS. With this new technology, known as recombinant influenza vaccine, a gene would be extracted from a flu virus and placed into an insect virus called baculovirus.

"We use cells from a species of caterpillar that is commonly referred to as the fall army worm (a common agricultural pest), the ones that eat the leaves in your back yard," Mr. Adams says. "We don't use live flu virus. The CDC publishes the genetic sequences of viruses on its Web site. Through genetic engineering technology, we are able to use that sequence to make the protein. We also extract genetic information from inactivated viruses that the CDC sends to us. From this information we make up a master virus bank. From this information we make up a master virus bank. We have hundreds of these frozen, and if one if them is for a virus for which we want to make a vaccine, we can begin manufacturing in two weeks. It usually takes several months to begin vaccine manufacturing using eggs. One thing we have learned from the novel H1N1 crisis is that egg technology can't adequately address a pandemic situation."

The company expects FDA approval sometime in late January for this product. Mr. Adams says that over the first few years, they expect to capture at least 18% of the world market.

Other companies, such as NanoBio, are working on vaccines that use adjuvants, or substances that modify vaccines to enhance the antigen's affect on immune response. NanoBio is developing a two-prong approach for influenza: a nasal prophylactic that contains no antigen and a vaccine using the company's nanoemulsion technology.

The vaccine uses the company's NanoStat technology as a delivery system and a universal adjuvant to elicit a much more robust immune response to what's traditionally been seen with injectable vaccines. An influenza vaccine using this technology is currently in human trials.

The influenza prophylactic product uses the company's nanoemulsion formulation without a vaccine antigen. When applied to the nose, viruses are killed before they can replicate and enter the lung, says Dave Peralta, VP, chief operating and chief financial officer at NanoBio.

"We could potentially provide a strain-independent influenza prophylactic while a vaccine is being developed," he says. "It would be applied via nasal spray or gel to provide protection to those who have high exposure to the virus. The initial interest has been for healthcare workers or people who are immunocompromised."

Mr. Peralta says their adjuvant product may have another benefit for pandemic infections. Animal studies have shown the nanoemulsion adjuvant to provide cross-protection against influenza strains not in the vaccine.

"Today's flu vaccines are strains of the

influenza virus that are decided upon by the CDC, and the vaccine manufacturers make the vaccine with those strains," he says. "The question is when individuals are exposed to another strain, are they protected? With our adjuvant we've seen very strong cross-protection against similar but not identical strains. This can be very important in a flu season where there are mutations of a virus that weren't predicted. That is certainly the case in a pandemic."

While adjuvant-based vaccines have been developed by the leading manufacturers and have been used in Europe since 1997, U.S. regulators have concerns about the safety of such vaccines. Currently, no adjuvant-based vaccines are approved for use in the United States.

"Our belief at GSK is that the adjuvants hold a strong benefit, which is the reason why the WHO and many other European countries have taken on GSK's adjuvant vaccines as their preferred vaccine," Mr. Lammers says. "The concern for U.S. regulators is that there hasn't been a great deal of patient exposure with a particular adjuvant. There is a desire to see additional safety information."

On Dec. 1, 2009, the WHO awarded prequalification for global use of GSK's Arepanrix, an adjuvanted H1N1 pandemic vaccine. The company has an agreement with the WHO to donate 50 million doses of its adjuvanted pandemic H1N1 influenza vaccine to the WHO for the distribution to developing countries most in need.

H1N1 TREATMENT

H1N1 is truly two different diseases, says Geert Kersten, CEO of Cel-Sci Corp.

"About 99% will get a little sick and be sick for a week or two," he says. "In 1% of cases, people will get horribly sick and many of those will need to be hospitalized. Once they are hospitalized, there are only antiviral drugs available for treatment and those tend to work only in the first few days of the infection. The rest of the patients will fight for their lives and, as we have already seen, a good number will die."

Mr. Kersten says antivirals only work within the first two or three days of a viral infection before the body is completely overwhelmed with masses of virus.

"At that point, what is needed is immunotherapy," he says "What is so unique about H1N1 is that people don't die from the virus; they die from an excessive immune response. The virus goes into the lungs. In young people the inflammation can be so great, it's as if the immune system carpet bombs the infected area. In this case, the body's immune response to the virus not just wipes out infected cells but lots of healthy cells as well. People die because their lung cells are being destroyed by their own immune systems."

Cel-Sci's technology, LEAPs, has been shown to reprogram an immune response. Now the company is testing the technology with the H1N1 virus to develop a therapeutic vaccine. In November 2009 Cel-Sci began a clinical study for hospitalized H1N1 patients at The Johns Hopkins University School of Medicine. This initial study will involve taking blood from 20 hospitalized, laboratory-confirmed H1N1 patients and activating their cells with the LEAPS-H1N1 investigational therapy in order to assess the cells' response as the basis for the planned future treatment of this patient population.

"We're focusing on the parts of the virus that don't mutate, otherwise we'd have to worry about developing a new product next year," Mr. Kersten says. "We have a peptide attachment that acts like the ruder of a ship and that helps to reprogram the immune system. It tells the immune system how to process the epitope that we're giving as a vaccine. This approach allows us to change the immune response to a targeted anti-virus immune response without the induction of pro inflammatory cytokines. This way, we can get the proper immune response without the massive inflammation, and without the peripheral damage." ✦

We make flu vaccines with different strains every year, and H1N1 was just another strain of the flu in terms of manufacturing a vaccine. This wasn't well-understood by the public.

DEBRA DRANE
CSL Biotherapies

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

EXPERTS ON THIS TOPIC

DANIEL D. ADAMS. President and CEO, Protein Sciences Corp., which develops and commercializes vaccines and biopharmaceuticals using its patented manufacturing platform. For more information, visit proteinsciences.com.

DEBRA DRANE. Senior VP, R&D, CSL Biotherapies, a leading manufacturer of influenza vaccines. For more information, visit cslbiotherapies-us.com.

TONY ESTRELLA. Chief Operating Officer and Co-founder HealthiNation, which produces health video programs that cover disease and condition education, along with patient stories, health tips, original series, and healthy lifestyle programs. For more information, visit healthination.com.

GEERT KERSTEN. CEO, Cel-Sci Corp., which is dedicated to improving the treatment of cancer and other diseases by unleashing the power of the immune system. For more information, visit cel-sci.com.

PETER LAMMERS. VP, Vaccines, GlaxoSmithKline, a leading pharmaceutical and healthcare company. For more information, visit us.gsk.com.

TERRI MADISON, Ph.D., MPH. President, i3 Drug Safety, which provides the data and services to help meet safety surveillance and support risk management programs. For more information, visit i3global.com.

DAVE PERALTA. VP, Chief Operating and Chief Financial Officer, NanoBio Corp., a biopharmaceutical company developing dermatological products, anti-infective treatments, and intranasal vaccines derived from its patented NanoStat technology. For more information, visit nanobio.com.