Getting New Influenza Vaccines Developed and Marketed

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The Swine flu scare has certainly arrived, though whether the much-feared pandemic will eventually materialize is far from certain.¹ Even if the current Swine flu infection now well-established on a path of international spread produces few deaths, fails to achieve epidemic proportions in the U.S., significantly disrupt our economy or overwhelm our health system,² the episode does provide a perfect backdrop for a timely review of some basic information about vaccines, vaccine production, and approval for marketing.

Vaccines and Vaccine Manufacturing

Vaccines are molecules which individuals either ingest, or are injected with, in order to stimulate their immune systems so that growth of pathogens, such as bacteria or viruses, may either be curtailed or, ideally, prevented.³ A wide array of vaccines, particularly childhood vaccines, are already on the U.S. market and comprise a diverse array of different types of vaccines including live whole virus vaccines, killed vaccines, inactive attenuated viruses (IATV), live attenuated vaccines (LAV), recombinant virus vaccines, and anti-bacterial DNA vaccines.⁴

Established and well-known vaccines include the polio virus vaccine and the decades-old, highly-effective childhood vaccines against generally non-fatal viral illnesses such as measles, mumps, or rubella or potentially lethal bacterial infections such as tetanus, pertussis, or diphtheria. These vaccines are generally accepted and have negligible side effects.⁵ More recently developed vaccines include the politically controversial vaccine against the human papillomavirus and highly experimental vaccines such as those against anthrax proposed for U.S. military personnel which were not certified as either safe or effective by FDA.⁶ In between these two extremes are the influenza vaccines. Flu vaccines are manufactured from scratch every year and are generally safe though not without the potential for serious side effects, as was the case with the development of Guillian-Barre syndrome following administration of the vaccine for the previous Swine Flu epidemic in the 1976.⁷ Flu vaccine effectiveness varies greatly from year to year depending upon both the manufacturing process used and whether the particular flu strain

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³ Edward Mortimer, Immunization Against Infectious Disease, 200 SCIENCE 902 (1978).
⁵ Mortimer, supra note 3.
the vaccine was developed against turns out to be the correct one.\textsuperscript{8} Influenza vaccine production has not been without significant controversy: problems with meeting U.S. domestic consumer demand as well as bacterial contamination from unsanitary manufacturing conditions were widely reported at Chiron Corporation several years ago\textsuperscript{9} and resulted in Congressional testimony over the vulnerability of U.S. domestic flu vaccine manufacturing safety and capacity.

Despite this recent government inquiry and concerns over whether there is enough vaccine manufacturing capacity to meet demands if a serious influenza pandemic were to strike the U.S., at the present time there are only four manufacturers which produce seasonal flu vaccine:\textsuperscript{10} Sanofi Pastuer, Inc.; Medimmune Vaccines, Inc.; Novartis Vaccine (formerly Chiron Corporation); and Glaxo SmithKline, Inc. Only two of these companies base the bulk of their manufacturing in the U.S., hence much of the U.S. flu vaccine supply is still manufactured overseas.\textsuperscript{11} Annual projected doses and flu vaccine products for these four manufacturers for a recent influenza season are in the table\textsuperscript{12} below, and demonstrate that the combined output of all manufacturers in a given year is well-below the number of doses required should most of the U.S.’s 300 million-plus citizens require immunization.

\begin{table}[h]
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\begin{tabular}{|l|l|l|l|}
\hline
Manufacturer & Doses 2007 Season & Vaccine & Age Indication \\
\hline
Sanofi-Pasteur & 50 million & Fluzone® Inactivated TIV & 6 mos or older \\
\hline
MedImmune & 3 million & FluMist™ LAIV & Healthy persons \\
\hline
Novartis & 28 million & Fluvirin™ TIV & 4 yrs or older \\
\hline
GlaxoSmithKline & 32 million & Fluarix/ FluLaval™ Inactivated TIV & 18 yrs or older \\
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\end{tabular}
\caption{Influenza Vaccine Manufacturers for 2007 Season}
\end{table}

\textsuperscript{8} Lawrence O. Gostin, Medical Countermeasures for Pandemic Influenza: Ethics and the Law, 295 NEW ENG. J. MED. 554 (2006).


\textsuperscript{10} See Themedica, supra note 4.


Given this predictable limitation in vaccine manufacturing capacity, it should come as no surprise that some wealthy nations have already inked “preproduction contracts” to guarantee that they will have an adequate supply of swine flu vaccine should the need arise.\textsuperscript{13}

The Annual Seasonal Flu Vaccine Guessing Game

It takes about six months for a seasonal flu vaccine to get to the U.S. public once the decision to actually pursue development and distribution of a new vaccine is made.\textsuperscript{14} The decision to develop and distribute a seasonal flu vaccine is one made by the U.S. government: the President delegates authority to the Secretary of Health and Human Services (HHS), who acts through the Centers for Disease Control in Atlanta. The CDC in turn bases its recommendation for the annual decision on examination of extensive epidemiological and virology data on the likely virulence of the strains of influenza virus likely to reach the human population; the likely geographical source and species of such a jump to humans (i.e. will it be from Asia or elsewhere, from fowl or swine?); the likelihood of such an influenza causing an epidemic or a pandemic; and on information obtained from its close working relationship with the World Health Organization (WHO) which makes independent recommendations.

The decision by the government to “cook up” millions of doses of flu vaccine is a major public health initiative for the federal government and a challenge to the pharmaceutical industry.\textsuperscript{15} As this article is written the U.S. government has not yet decided whether to call for the development of a swine flu vaccine, but they are inching in that direction. The fear on the government’s part is that the particular strain of influenza now going around may ultimately prove as lethal as SARS and they do not want to be caught short while waiting for definitive data to materialize; for this reason the CDC has already set the wheels in motion.\textsuperscript{16} The essential first step in developing a new vaccine is getting examples of the isolated new viral strain (“seed stock”) to laboratories to begin growth of the influenza virus in eggs.\textsuperscript{17} The CDC has already sent samples of the new Swine Flu strain to more than ten government and academic laboratories in the U.S.\textsuperscript{18} The task of these laboratories will be to develop an influenza virus that “grows well in eggs and that, when injected into eggs along with a new strain like H1N1, will swap some of its genes with the new strain,”\textsuperscript{19} so that viral particles with the new strain on the outside may be selected and ultimately used to create an injectable vaccine that will produce immunity in

\textsuperscript{17} Denise Grady, \textit{Cooking Up Millions of Viruses for a New Vaccine}, N.Y. TIMES, May 5, 2009, at A12
\textsuperscript{18} Id.
\textsuperscript{19} Id.
Despite the collected efforts of some of the finest influenza virus minds in the world at CDC and WHO, the decision-making process for vaccine strain selection, production, and whether to recommend widespread or selective vaccination is a complicated one and fraught with possible missteps. For example, the decisions and decision-making involved in 2006 Avian Influenza A (H5N1) vaccine selection have been debated in light of the failure of an epidemic with significant mortality to materialize as well as the limited effectiveness of the manufactured vaccine against the strain which actually caused the majority of infections in the U.S. that year. The 2009 Swine Flu epidemic is another example of how difficult it is for authorities to predict the likely animal source and point of origin of an influenza pandemic: both the primary source (pigs) and site of origin (Mexico) were apparent surprises to the WHO and CDC.

These surprises notwithstanding, health officials are now taking some comfort in several facts which are operating against the likelihood of a much-feared pandemic with high death rates: (1) the current Swine Flu infection does not appear to be as lethal as once feared; and (2) the molecular biology of the current viral strain is very similar to that of influenza strains which have both produced relatively mild infections and for which extensive vaccine manufacturing capacity already exists. In particular, the current H1N1 flu strain is dissimilar from the 1918 Avian flu strain which killed more than 50 million people worldwide.

How Fast Can FDA Approve New Vaccines for U.S. Marketing?

Once the decision to develop a flu vaccine is made, manufacture of the strain-specific vaccine undertaken by industry and plans for widespread vaccination implemented, manufacturers of any potential vaccine must deal with the U.S. Food and Drug Administration (FDA). Because vaccines are biological drug products they fall under the jurisdiction of the Center for Biologics Evaluation and Research (CBER) at FDA. Although CBER is one of the smallest of the five Centers at FDA it has a highly motivated and trained staff, many of whom hold joint appointments at the National Institutes of Health, as well as vast experience with both vaccine products and dealing with potential infectious disease pandemics.

A manufacturer of a new vaccine for treatment of Swine Flu would submit a Biologics Licensing Application (BLA) to CBER which would then be assigned to a team of scientists and physicians for a priority review of manufacturing practice and safety and efficacy data. Although a new marketing application on priority review has a six-month approval clock, it is possible and perhaps even likely that the turnaround time for

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20 Id.
22 See Gostin, supra note 8.
24 Id.
approval on the FDA side would only be a matter of weeks. Once approved, the manufacturer of the new vaccine would be cleared to sell the vaccine to consumers, clinics, and hospitals. The FDA plays two on-going roles to ensure the safety of vaccines: it evaluates and approves the results of tests on the first vaccine batch “model,” and then repeatedly examines successive batches produced for injection into humans to ensure that they mimic the batch “model” as closely as possible. This continual involvement is necessary because, as the byproduct of natural biologic processes, successive batches of vaccine may differ in composition and thus effectiveness.

Prevention vs. Treatment: Vaccine Not the Only Weapon This Time

Fortunately, the current Swine Flu infestation appears to differ from recent flu infestations in at least one important aspect: the anti-viral medication Tamiflu appears to be highly effective in the treatment of this ongoing influenza as opposed to epidemics in recent years when the drug was of limited or no effectiveness. The availability of a second drug as an effective anti-viral therapy for established Swine Flu infections dramatically decreases the reliance on a Swine Flu vaccine alone as the sole bulwark against morbidity and mortality from the infection and significantly increases therapeutic options for U.S. health care providers should problems with producing adequate amounts of the Swine Flu vaccine undergoing development arise. The advantage of an anti-viral medication, such as Tamiflu, is that even if efforts to prevent Swine Flu infection fail there are therapeutic options for treatment of flu and flu symptoms in infected individuals. Of course, this raises the separate issue of whether the U.S. domestic supply of Tamiflu is destined for a shortfall as well. Based on recent reports in the media, it would appear that the U.S. has not stockpiled Tamiflu to the same degree as other industrialized nations, Great Britain in particular, and may not be so well equipped for influenza disease treatment, as opposed to prevention, as other countries.

One Final Note

Perhaps the most interesting international public health take home message from the current Swine flu episode may be gleaned from a recent commentary in The New York Times pointing out the difference between the manner in which the Mexican government has handled the current Swine flu outbreak with the way in which the Chinese government handled the SARS crisis in 2002. At a point in the epidemic when the trajectory of the disease and patient mortality were both unknowns, but the worst was feared, unlike the Chinese government the Mexican government did not try to deny there was an outbreak, was not slow in attempting to combat its spread nor did they resist cooperation with foreign investigators. Perhaps some lessons have been learned after all.

26 Id.
Health Law Perspectives (May 2009), available at:
http://www.law.uh.edu/healthlaw/perspectives/homepage.asp