

Removing Barriers to Global Pandemic Influenza Vaccination

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This article clarifies the regulatory issues surrounding influenza pandemic vaccine for the larger policy community and describes the need for regulatory harmonization. Vaccination would save lives in an influenza pandemic, but a lack of global manufacturing capacity will leave most of the world without access to vaccine. Capacity can be expanded if governments harmonize their regulatory policies. This article details the regulatory approaches taken by the United States, the European Union, and Japan for pandemic vaccine development, three regions that produce the majority of the world's seasonal influenza vaccine. They should quickly converge on regulatory requirements, intellectual property considerations, the use of recombinant DNA techniques for vaccine production, and technical issues about the composition of pandemic vaccine.

IN AN INFLUENZA PANDEMIC, most of the world will not get vaccine. Vaccination would be the best way to prevent infection and save lives, but there simply won't be enough. The United States, France, Australia, Canada, Japan, and other wealthy countries have contracted with manufacturers to produce pandemic vaccine for their citizens, but their demand will quickly exceed the global production capacity. The manufacturing capacity for seasonal influenza vaccine is only about 300 million doses per year globally, and the capacity for pandemic influenza vaccine will be even less.¹

Faced with certain shortages, some governments and vaccine manufacturers are attempting to expand production capacity. They are conducting clinical trials of new formulations that boost the effectiveness of smaller doses of vaccine in order to stretch supply, and they are constructing additional manufacturing plants. However, there is another step that would increase vaccine availability: Governments can harmonize their regulatory policies for pandemic vaccine. Shared requirements would save time in production and would streamline global access. Clinical trials would not have to be wastefully duplicated, and vaccine manufacturers would not have to submit different applications for the same product to each regulatory agency. According to a World Health Organization (WHO) meeting of influenza vaccine manufacturers, national licensing

agencies, and government representatives, harmonizing regulatory requirements would facilitate global vaccine access—an important consideration for non-vaccine-producing countries in a pandemic.²

This article will illuminate the benefits and challenges of regulatory harmonization and will clarify the regulatory issues surrounding pandemic vaccine for the larger policy community. To this end, this article examines the regulatory approaches taken by the United States, the European Union (EU), and Japan for pandemic vaccine. These three regions produce the vast majority of new medicines and the majority of seasonal influenza vaccine.³ If they were to harmonize their regulatory procedures, it would streamline access to pandemic vaccine well beyond their spheres.

The U.S., the EU, and Japan have worked together in the past; they form the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), a joint regulatory-industry initiative “to improve, through harmonization, the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the United States, in order to make these products available to patients with a minimum of delay.”³

These regions also have taken the first step toward regulatory harmonization for pandemic influenza. With the

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strong support of WHO, regulatory officials from the U.S., Europe, Japan, and Canada met in Ottawa in March 2006 to discuss possible regulatory convergence on pandemic influenza vaccine, with another meeting planned for June 2006. Discussions are at an early stage, and vaccine manufacturers' input has not yet been sought (personal communication, Jesse Goodman, Director, CBER, FDA, March 31, 2006). Going forward, the urgency of a possible pandemic demands that regulatory agencies pursue a transparent, inclusive, and *accelerated* process toward harmonization of pandemic vaccine regulations. These initial meetings of regulators should be the jumping-off point to accomplish this public health good and should be made a high priority.

REGULATORY AGENCIES SHOULD USE THE SAME REQUIREMENTS

A pandemic vaccine will be designed to protect against the influenza virus causing the pandemic, whether it is H5N1 avian influenza or another viral strain. The safety and efficacy of the vaccine will be evaluated by the appropriate regulatory agencies within a country. If the agency approves the vaccine, as well as the methods used by the manufacturer, the pandemic vaccine can be marketed and purchased.

Unfortunately, the global influenza vaccine manufacturing base is tiny, and countries do not have many options for purchasing. In 2000, only nine vaccine companies produced 85% of the world's supply of seasonal influenza vaccine.⁴ Several manufacturers of pandemic vaccine will produce more than one country's supply. For example, sanofi pasteur SA has already entered into pandemic vaccine contracts with the U.S., France, Australia, and "many other governments in Europe and worldwide, as well as with the international organizations."⁵ As each country has specific licensing requirements and regulations, the vaccine manufacturers must tailor their product to each country's regulatory framework. This wastes time that could be spent producing vaccine, it limits the entry of manufacturers into the global market, and it limits the ability to produce vaccine for the global population.^{1,6,7}

Harmonizing regulatory processes for pandemic vaccine would not cede regional control of the pharmaceutical approval process—the Food and Drug Administration (FDA) would still need to approve a vaccine for use in the United States, the European Medicines Agency (EMA) would need to approve products for the EU, and the Pharmaceuticals and Medical Devices Agency (PMDA) would need to approve the vaccine in Japan. However, if there were shared regulatory processes at these agencies, they would be able to use the same clinical trial data for

safety and efficacy testing of a pandemic influenza vaccine. The vaccine manufacturers would submit a common application to each regulatory agency for approval, and they would be held to common standards.

With harmonization, manufacturers could produce one pandemic vaccine for multiple markets, without delaying production for reasons that do not affect the quality, safety, or efficacy of the vaccine. Shared regulatory processes would eliminate duplicative clinical trial testing in order to satisfy different regulatory systems. Because clinical trials are expensive and take a long time, eliminating duplicative testing saves both time and money.^{6–10} Preclinical testing done in animals also would be streamlined to eliminate unnecessary duplication, thus cutting the costs and unnecessary use of experimental animals.⁸

For the U.S., harmonization of the regulatory processes for *seasonal* as well as pandemic influenza vaccines may help to prevent influenza vaccine shortages.⁹ In 2004–05, Chiron was found to have contamination problems at their production plant and could not supply influenza vaccine to the U.S. At the time, there were only two suppliers of injectable vaccine to the U.S.: Chiron and sanofi pasteur. Other vaccine manufacturers, including Solvay, GlaxoSmithKline, and ID BioMedical [now a division of GSK], were not then licensed by the FDA, so they could not market vaccine in the U.S. The U.S., then, was the only country that had a vaccine shortage, in large part because regulatory barriers to entering the U.S. market are perceived as being too high. For example, the FDA does not accept data from clinical trials performed without FDA monitoring, so a non-US-licensed vaccine manufacturer has to re-conduct clinical trials in order to market their vaccine in the U.S. (personal communication, Patrick Celis, EMA, September 6, 2005).⁹ In the 2004 influenza vaccine shortage, before GlaxoSmithKline could enter the U.S. seasonal influenza vaccine market, it had to conduct clinical trials with FDA monitoring, even though Fluarix had been tested for safety and efficacy, licensed, and used since 1992 in more than 70 countries, in more than 150 million doses.^{11–13}

In contrast to the U.S. situation, FDA-monitored trials are transferable from the United States to most European countries, providing an incentive to license U.S. vaccines for the European market, but not the other way around. In 2004, Lester Crawford, then Acting Commissioner of the FDA, testified, "Among the lessons we have learned from this year's events at Chiron is the need to enhance our international regulatory collaboration and harmonization efforts."¹⁴ The Government Accountability Office, the National Vaccine Program Office, and the National Vaccine Advisory Committee in the Department of Health and Human Services (DHHS) have called for regulatory harmonization for seasonal influenza vaccines to remove "artificial barriers" to the U.S. market.⁹

There are costs to harmonization: Manufacturers need to retool for the new standard, and governments need to adapt to the new regulations and train personnel.¹⁰ There also may be political challenges. For example, in 1991, ICH developed a standard for the length of chronic toxicity testing in animals. Prior to the negotiations, Japan and the U.S. required animal testing of at least 12-month's duration for new pharmaceuticals. The EU required only 6 months of testing. Eventually, they agreed on a 9-month maximum duration for testing, and the EU continued to accept a 6-month minimum. An official at the European Commission commented, "Europe was between a rock and a hard place on this one. There was no way politically that we could go to 9 months because we could potentially have undermined all the existing products on the market by saying that they were incorrectly tested."⁶ The differences among the U.S., EU, and Japanese regulatory approaches may have technical equivalence, but the political perceptions of safety may differ. Harmonizing pandemic vaccine regulations may face the same challenges.

Overall, however, harmonization would have many benefits: It creates a gold standard for product development, ensuring that people around the world have equivalent high-quality, safe, pure, potent, and efficacious vaccines, regardless of where those vaccines are made. It avoids wastes of time and money and lowers financial barriers to entry for all market participants.

VARYING REGULATORY APPROACHES

The U.S., Japan, and the EU have all made significant investments in their approaches to influenza vaccine development, which may give them fewer incentives for changing direction. However, creating a pandemic vaccine is an unprecedented project; if vaccine is needed, all methods for expanding vaccine supply should be considered. It is to be hoped that the uniqueness and urgency of the need for pandemic vaccine will result in fewer barriers to regulatory convergence than with other pharmaceuticals. This section describes how the U.S., the EU, and Japan have approached pandemic vaccine development and what major differences will need to be resolved.

Actors in Developing, Licensing, and Funding a Pandemic Vaccine

In Japan, the research, development, and production of pandemic vaccine is a national project, funded entirely by the government and conducted through the nation's four manufacturers of seasonal influenza vaccine: the Chemo-Sero-Therapeutic Research Institute (Kaketsuken); Biken, the Research Foundation for Microbial Diseases of Osaka University; Kitasato Institute; and Denka Seiken Co., Ltd. Only one of these companies, Kaketsuken, is a for-profit venture.² The companies do not usually work together on projects; this is a special case (personal communication, Hiroyuki Yokote, Regulatory Affairs, and Shuro Goto, Deputy General Manager of the Human Vaccine Production Department, Kaketsuken, the Chemo-Sero-Therapeutic Research Institute, November 4, 2005). The Japanese Ministry of Health, Labor, and Welfare (MHLW) is responsible for coordinating the research and development of the vaccine, and the Pharmaceuticals and Medical Devices Agency (PMDA) is responsible for approving the vaccine. Once a pandemic has started and the exact strain causing it is known, licensure will be on a "fast-track pathway" for priority groups.² There are no public plans for any of the national manufacturers to export vaccine in the case of a pandemic.

The U.S. also has used public funding to develop its pandemic vaccine, but, in contrast to Japan, it has relied on public-private partnerships with international vaccine manufacturers. Responsibility for the U.S. project rests primarily with the DHHS and the international vaccine manufacturers Chiron (Emeryville, Calif.) and sanofi pasteur SA (Lyon, France). DHHS is coordinating, funding, and regulating the vaccine project. Within DHHS, the major actors are the National Vaccine Program Office (NVPO); the Office of Public Health Emergency Preparedness (OPHEP); the National Institute of Allergy and Infectious Disease (NIAID), which is part of the National Institutes of Health; and the FDA, which will review pandemic vaccine applications and make decisions about whether a pandemic flu vaccine can be licensed for use. The FDA has formed a Rapid Response Team that will "facilitate the development and availability of safe and effective vaccines . . . [by] facilitating and evaluating studies that use new technologies."¹⁵ The U.S. has no public plans for exporting vaccine, but sanofi pasteur is already contracted to sell pandemic vaccine in other markets.⁵

Like the U.S., the EU has developed public-private partnerships for pandemic vaccine, but it has seemingly demanded the most from the vaccine manufacturers; they have to pay for most of the clinical trials and other developmental steps that the EU requires. The EU has dedicated some funds; in total, 12.4 million euros have been allocated for "the development of new vaccines, establishing surveillance networks, monitoring drug resistance and examining the use of antivirals."¹⁶ The European Medicines Agency (EMA), the EU equivalent of the FDA, has so far received an application for pandemic vaccine from GlaxoSmithKline Biologicals¹⁷ and from Chiron.¹⁸ Sanofi pasteur also is planning on submitting

an application through their work in FLUPAN, an EU-funded collaboration, using an H7N1 vaccine, another potential pandemic influenza strain.⁵ There are no public plans for the EU export of pandemic vaccine, but it is mostly the European manufacturers that currently export seasonal vaccine.⁴

Genetically Modified Organisms (GMO)

For technical reasons, the development of a pandemic vaccine will require a technique called “reverse genetics” (see sidebar). The use of this technique is not a regulatory barrier for Japan or the U.S., and it requires no additional tests or clinical trials. However, the use of reverse genetics is a problem for licensing pandemic vaccine in the EU, as it would be considered a genetically modified organism (GMO), and it would be subject to a higher regulatory burden than other vaccines. Reverse genetics–engineered viruses can be “used only in facilities that meet high-level biosafety requirements that not all companies currently have.”¹⁹ Upgrading facilities takes at least one year and is expensive.²

While some pharmaceutical products can gain approval in one EU country without extension to the whole EU—for example, a drug can be approved in Italy for residents of Italy alone—this is not possible for GMO products (personal communication, Patrick Celis, EMEA, September 6, 2005). GMOs are regulated by the EU in a centralized procedure at the EMEA, not by each regulatory authority in individual countries that make up the Union. Only after EMEA approval can GMO products be marketed in every country of the Union.

As it stands, however, few vaccine manufacturers are able to meet the EU GMO biosafety requirements, and there are signs of discord in the Union regarding this policy. Hungary, a member of the EU, and Romania, a candidate country for EU enlargement, have decided to ignore the EMEA altogether. The Hungarian regulatory authorities have approved a vaccine made by Omnivest, a Hungarian company, which contains alum (an immune booster, or adjuvant) and is made with reverse genetics.^{20,21} Romania also is interested in manufacturing the Hungarian vaccine.²²

WHO has put forward recommendations for the biosafety requirements of pandemic vaccine, which may be a workable compromise for harmonization on GMOs.^{23,24}

Technical Considerations for Pandemic Vaccine Development

All pandemic vaccines are not likely to be the same; there may be differences in the dose, formulation, route of administration, and additives. These differences may affect the licensure of pandemic vaccines by each regulatory agency.

For the past several years, FDA officials have outlined the steps potential pandemic vaccine manufacturers should take for FDA approval, and in March 2006, they published guidance on the clinical data needed for licensure of a pandemic vaccine.²⁵ Their message: The regulatory difficulties required for licensure depend on how similar the pandemic vaccine is to the seasonal influenza vaccine (for a description of the seasonal influenza vaccine production process, see sidebar). If the potential pandemic vaccine was manufactured and delivered using methods similar to those for a normal seasonal influenza vaccine, and if it was made by a currently U.S.-licensed vaccine manufacturer, the vaccine would just be considered a “strain change.” For example, the potential pandemic strain H5N1 would replace the seasonal H3N2 strain.^{2,26,27} The FDA also would want the manufacturers to provide clinical data demonstrating that the dose and regimen of their pandemic vaccine would likely be protective in a pandemic.²⁵

However, if the potential pandemic vaccine were to significantly differ from the seasonal influenza vaccine, it would undergo regulatory review as a “new product,” and the regulatory burdens would be considerably greater than for a seasonal influenza vaccine. A potential pandemic vaccine could differ from the seasonal vaccine in a number of ways, potentially triggering a more stringent review process: It could require more than 45 micrograms of antigen, the influenza virus–derived material that triggers a protective immune response; it could require an adjuvant, an additive that boosts the immune response; or it could be a “whole” versus a “split” vaccine (see sidebar), which also may boost immune responses to the vaccine.²⁸

NIAID-sponsored clinical trials determined that a simple change to the H5N1 strain from a currently licensed influenza vaccine would not be protective. The preliminary data were disappointing: The most protective dose of vaccine tested was two 90-microgram doses of the H5N1 vaccine; 54% of people who received that dose developed an immune response that is predictive of protection.²⁹ Vaccinees would therefore need *four times* the amount of antigen in a typical flu shot. The supply of H5N1 vaccine that NIAID ordered was hoped to cover 2 million people at 15 $\mu\text{g}/\text{dose}$.² Instead, it would only protect about 95,000 people.

NIAID is now researching “antigen-sparing” methods to boost supply, such as intradermal delivery of the vaccine (instead of getting a shot in the arm, the shot would be in the top layers of skin) and the use of adjuvants. Chiron was contracted by NIAID to test their proprietary adjuvant MF59, which is already licensed in Italy, with the potential pandemic influenza strain H9N2. They found that 3.75 micrograms/dose was sufficient to stimulate immunity.³⁰ NIAID also recently entered into a con-

Manufacturing Seasonal Influenza Vaccine

Each year the circulating flu virus is different, so the seasonal flu vaccines need to be different as well. The effectiveness of the flu vaccine depends on which influenza strains are selected to be the basis of that year's vaccine.

Three different flu viruses form the basis of the vaccine—two influenza A viruses, and one influenza B virus. Type A changes frequently and causes large outbreaks; type B does not change as frequently and causes smaller outbreaks. Because type C usually causes a milder illness, it is not included in the vaccine. Each vaccine has 45 micrograms of viral material—15 micrograms from each of the three viral strains. This viral material is called an “antigen,” because it stimulates the immune system to respond. The specific response of a person's immune system to the antigen is what makes this vaccine effective.

The process of picking which influenza A and B strains form the vaccine starts with surveillance. Global surveillance of emerging flu strains is coordinated by the WHO Global Influenza Surveillance Network. This network consists of 112 national influenza centers in 83 countries. They process more than 175,000 patient samples per year, and submit more than 2,000 viruses to the WHO Collaborating Centers located in the U.S. (Atlanta), UK, Australia, and Tokyo. The viruses and accompanying clinical data are analyzed to determine which viruses are currently infecting people around the world and which cause the most serious disease.

For the U.S., the Vaccines and Related Biological Products Advisory Committee (VRBPAC) at the FDA makes a recommendation for at least one of the viruses to be included in the vaccine, in January of each year. In February, health officials from the WHO collaborating centers, including the CDC and FDA, review the results of laboratory and clinical studies and make recommendations about the composition of the flu vaccine for the northern hemisphere. In March, the VRBPAC meets again to finalize the recommendations for the U.S. influenza vaccine. The FDA gives these seed strains to vaccine manufacturers to start vaccine production.

About 6 months before vaccine production starts, manufacturers order specially grown, clean chicken eggs. Millions of the 11-day-old fertilized eggs are injected with the influenza seed strains. The three seed strain viruses are grown separately. After several days of incubation, multiplying virus fills the eggs. Machines open the eggs and harvest the contents.

The influenza virus is purified several times to separate the virus from the egg proteins. The virus is chemically inactivated, so that it will not *cause* influenza.

Then the virus is “split” or broken into fragments, which tends to reduce side effects in the people who get the vaccine. The three seed strain viruses are grown separately, but they are mixed together to make one vaccine. The vaccine is then packaged into vials and distributed to vaccine providers in time for September vaccination campaigns.

The manufacturers and the FDA test the vaccine to make sure that it is safe to use for vaccination. This includes sampling some vaccine vials, verifying that the vials were filled under sterile conditions, and finding no contamination.

A problem or accident in any step of vaccine production can lead to significant delays. Vaccine production depends on how early the strains are selected for production, how well the strains grow in the fertilized chicken eggs, and whether the production process and the vaccine meet regulatory approval. There is little room for manufacturing errors and no potential to scale up the process if there is an increased demand for vaccine.

The vaccine can be produced in other ways, but these methods do not yet have regulatory approval in the U.S. Influenza strains now grown in eggs can be grown in test tubes using human, monkey, or dog cells developed expressly for this purpose. Other vaccines, such as polio vaccine and the modern smallpox vaccine, are made this way. Abandoning chicken egg cultures for a more modern process has several potential advantages, especially in the ability to scale up the process. Currently, because the eggs have to be ordered months in advance, more cannot be delivered if there is a need for more vaccine; animal cells are more readily available and can be grown to large numbers quickly.

Using animal cells to culture the flu vaccine would also allow the vaccine production process to be started closer to flu season, which would increase the likelihood of a “match” between the vaccine and the year's circulating flu strains. An animal cell culture system for producing influenza vaccines has gone through Phase II FDA clinical trials.

Another potential vaccine process could use the biotechnology technique of reverse genetics to “cut and paste” the pieces of influenza needed to go into a vaccine. This process is being developed to create a vaccine for avian influenza. It has the potential to be a faster and safer method of producing flu vaccines than the traditional egg-based vaccine. However, reverse genetics methods are patented. The commercial implications of producing a vaccine using proprietary methods are as yet unclear to vaccine manufacturers.

tract with MedImmune, which makes FluMist, an attenuated live influenza vaccine, which is developing an investigational live attenuated pandemic influenza vaccine.³¹

In contrast to the U.S. FDA, EU EMEA officials have for years considered a potential pandemic flu vaccine to be a new product and not a “strain change” from the ordinary flu vaccine (personal communication, Patrick Celis, EMEA, September 6, 2005). However, EMEA rules are typically more stringent than those of the U.S. FDA for seasonal vaccines; manufacturers have to conduct clinical trials yearly, with each strain change.

EU officials have asked potential pandemic vaccine manufacturers to submit a “mock-up” vaccine for approval by the EMEA. Clinical trials with the mock-up need to demonstrate safety, immunogenicity, dose, and dosing schedule.² The mock-up vaccines must contain viral antigens to which humans have not been previously exposed (such as H5N1, H9N2, etc.). If a pandemic threat is declared, the manufacturer that has approval for its mock-up vaccine can then start producing vaccine with the correct strain. They will have to provide limited “quality” data to EMEA based on the new pandemic strain. Each vaccine will receive fast-track approval within 3 days, and companies will have to gather safety, immunogenicity, and effectiveness data during clinical use.¹⁹

The EU received its first pandemic vaccine application in January 2006, from GlaxoSmithKline Biologicals,¹⁷ and a second application from Chiron a month later.¹⁸ Sanofi pasteur also is conducting clinical trials at three sites in France, to evaluate the safety and immunogenicity of the vaccine and to “determine its optimal formulation, especially concerning the adjuvant.”¹⁵ Results from these trials will be used to prepare a “mock-up” for submission to EMEA. Sanofi is also participating in FLUPAN, an EU-funded collaboration intended to improve pandemic preparedness in the EU, using an H7N1 vaccine.⁶

For Japan, the project is still in the pre-clinical stage. Logistically, they expect that the vaccine will take two separate shots to be immunogenic, and that it will need an adjuvant (such as alum), though both adjuvanted and nonadjuvanted vaccines are likely to be tested. Their work suggests that an alum whole virus vaccine would provide the highest immunogenicity.² At the time of this writing, there is little public information available on their progress.

INTELLECTUAL PROPERTY: AN ADDITIONAL CONCERN

Reverse genetics is a proprietary technique. Though intellectual property issues “should not impede seed development and clinical trials” for pandemic vaccine, they

will have cost implications if the vaccines are commercialized.² There are other potential intellectual property issues involved in pandemic vaccine development, such as proprietary adjuvants.

Intellectual property issues often arise in the development of health products. However, this issue merits special consideration for pandemic influenza, because if a vaccine is needed, it would need to be produced quickly for a global market, and the pressures of time and politics may lead governments to invoke compulsory licenses for patented technologies. These issues need to be resolved by companies and governments before an influenza pandemic occurs.

NEXT STEPS

“Never before had a pandemic been preceded by a warning signal, such as that sounded by the H5N1 avian influenza outbreaks in Asia; never before had industry, regulatory agencies, and governments had an opportunity to find joint solutions on the possible brink of a pandemic.”

World Health Organization, 2005²

Whether an influenza pandemic occurs next week or in the next decade, regulatory harmonization for a pandemic flu vaccine could speed the process of delivering safe, tested vaccine to all parts of the world—a shared goal of the U.S., EU, and Japanese regulatory agencies. While each region has taken a different approach, none has obvious superiority. There are many benefits to each region and to the world for a harmonized marketing application for pandemic vaccine. The current disharmony is a barrier and a burden for companies, governments, and, ultimately, vaccine recipients.

In addition to the steps that the U.S., the EU, and Japan have taken, press releases indicate that Australia has contracted with CSL Limited,³² sanofi pasteur⁵ Canada has contracted with ID Biomedical Corp (now part of GSK),^{33,34} and Norway has contracted with Solvay Pharmaceuticals.^{35,36} Baxter,³⁷ Acambis, and GSK also will likely manufacture pandemic flu vaccine. A harmonization process should include these countries and manufacturers.

This article has focused on the U.S., the EU, and Japan because they produce most of the world’s seasonal influenza vaccine, and they have worked together in the past, as part of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use. While the Conference has dealt mostly with technical considerations, it could be the basis of a global harmonization process for pandemic as well as seasonal flu vaccine.

Alternatively, the governments of vaccine-producing countries may pursue a separate process for harmonization of pandemic vaccine regulations. Regulatory officials from the U.S., Europe, Japan, and Canada, as well as WHO officials, met in Ottawa in March 2006 to discuss possible regulatory convergence on pandemic influenza vaccine. There is another meeting planned for June 2006, though at this point discussions do not include vaccine manufacturers (personal communication, Jesse Goodman, Director, CBER, FDA, March 31, 2006). These meetings should be made a high priority. The urgency of a possible pandemic, as well as the current level of investment in pandemic vaccine development, demand that regulatory agencies pursue a transparent, inclusive, and *accelerated* process to harmonize pandemic vaccine regulations. These initial meetings of regulators should be the jump-off point to accomplish this public health good.

Pandemic vaccine development is largely driven by only a few countries; thus, it is up to them to ensure an excess supply, with the goal of an equitable distribution of vaccines in a pandemic. Many countries do not have vaccine manufacturers within their borders or under contract—including Indonesia, Thailand, and all of Africa. In order for people in these countries to have vaccine, vaccine manufacturers will need to ramp up production of safe, effective vaccines without delay.

Even with harmonization, global access to pandemic influenza vaccine—the best way to prevent infection and save lives—will be a tremendous challenge. The most effective vaccine cannot be formulated until the specific influenza strain causing harm is known. Even if vaccine manufacturers start production as soon as possible after the epidemic starts, they will start the race well behind the virus. But there is reason for hope: In past pandemics, there were waves of infection, and it was the later waves that caused the highest numbers of morbidity and mortality.¹⁹ If the next pandemic is similar, many would benefit from a vaccine, even if it is not available immediately. It is worth every effort to shorten the time the world would wait.

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