



Testimony
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Influenza Vaccine: The State of Readiness
for the 2005-2006 Flu Season

Statement of

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INTRODUCTION

Mr. Chairman and members of the Committee, I am Dr. Jesse Goodman, Director of the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA) and also a practicing infectious diseases specialist. I appreciate the opportunity to update you on FDA's recent and ongoing efforts, in collaboration with other Department of Health and Human Services (HHS) agencies and with the private sector, to address issues surrounding the influenza vaccine supply needs for the next flu season and to do what we can to help prevent the problems encountered last season from recurring. These efforts should also better prepare us for the next global influenza pandemic.

FDA is responsible for the regulation and oversight of vaccines in the United States. Vaccines are among our most important and cost-effective medical interventions, preventing disease in those who receive them and reducing the spread and risk of infections through our communities. I want to assure the American public that the safety, effectiveness and availability of vaccines are among FDA's highest priorities and that we work closely with DHHS, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), as well as with manufacturers, in addressing this important area of public health preparedness.

THE 2004-2005 INFLUENZA SEASON

As you know, influenza vaccine is unique because its active ingredients – the virus strains used to develop the vaccine – change almost every year.

Therefore, manufacturers must produce tens of millions of doses of a new vaccine each year. While promising technologies such as cell culture and recombinant protein and DNA-based influenza vaccines are in the research and development stages and we are working with our HHS colleagues to advance their development, the most efficient vaccine production methods currently available involve the use of millions of live, non-sterile eggs to grow three different strains of influenza viruses annually. This is a complex process that spans several months during which manufacturers cultivate the appropriate strains to make the vaccine. These factors present an enormous challenge for manufacturers and create uncertainty for vaccine supply.

Each year, FDA begins working with manufacturers at the earliest stages of vaccine development, and we continue to assist them throughout the production phase. We do this not only through our regulatory evaluations, but also by providing needed influenza strains and standards that can be used for efficient manufacturing. Specifically, we provide reagents to assure that the vaccine is potent and we further evaluate the vaccine through the use and review of laboratory tests that help assure the safety and efficacy of the vaccine.

Throughout this process, FDA frequently discusses technical and manufacturing issues with manufacturers.

Influenza vaccine is highly cost-effective and beneficial to the public. Over the last decade, health care providers, CDC and others have been very successful in expanding the number of Americans who receive the vaccine. However, as we have emphasized in previous Congressional testimony, the influenza vaccine market is very fragile because the increasing demand has been coupled with a decline in the number of U.S.-based and U.S.-licensed manufacturers.

Importantly, the market returns for producing this and many other vaccines are usually minimal, while the financial and other risks involved are great. Further, vaccine manufacturing requires careful and comprehensive controls, a complex and sometimes unpredictable manufacturing process and highly specialized facilities that can be expensive to maintain and update. For the 2004-2005 season, only three U.S. licensed manufacturers began production of influenza virus vaccine: Chiron Corporation and Aventis Pasteur produced inactivated vaccine, the form currently used for most high-risk individuals, while MedImmune, Inc. manufactured FluMist, a recently-approved, live, attenuated (weakened and safe) influenza vaccine.

As you know, on October 5, 2004, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) suspended Chiron's license to manufacture influenza vaccine due to good manufacturing practice deficiencies that led to sterility failures in filled vials of the vaccine. FDA and MHRA's review of Chiron's investigation of the root cause of the company's sterility failures and

our own review and inspections of their facility pointed to problems that led FDA to the conclusion that the sterility, and therefore safety, of the vaccine Chiron produced for the 2004-2005 influenza season could not be assured.

Efforts to Obtain Additional Vaccine

The loss of Chiron's planned contribution to the U.S. influenza vaccine supply posed serious challenges. FDA worked with urgency, aggressiveness and in close coordination with CDC and other components of HHS and the private sector to explore all viable options to secure additional doses. FDA worked with sanofi pasteur and MedImmune to secure approximately five million additional doses of U.S. licensed vaccine. Sanofi pasteur increased production to 58 million doses of Fluzone, and MedImmune scaled up to produce three million doses of FluMist. FluMist is currently recommended for healthy individuals 5 to 49 years of age, and therefore provides an option for those who would not receive vaccine under CDC's priority guidelines, such as the U.S. military. Therefore, to expand further the supply of vaccine to those with the greatest need, then-Secretary Thompson, in cooperation with the Department of Defense, announced that the military would maximize its use of FluMist as a substitute for inactivated vaccine, making an additional 200,000 doses of injectable vaccine available to HHS for high-risk civilian populations. Because sanofi pasteur produces pediatric dosage forms of vaccine for the U.S. market, the supply of vaccine available for high-risk children was, fortunately, not reduced. Through these collaborative efforts, manufacturers increased the available supply of

licensed influenza vaccine for the U.S. population to 61 million doses for this past influenza season, compared with approximately 83 million doses distributed in 2003-2004 and in 2002-2003, 77 million doses in 2001-2002 and 70 million doses in 2000-2001.

Because there was a concern that the need and demand could still outstrip supply, particularly if we faced a severe influenza season, we sought additional doses of vaccine that could be safely used in an emergency. Thus, in addition to enhancing the supplies of vaccine approved for use in the U.S., we were able to rapidly identify suppliers of approximately five million doses of additional vaccine, licensed in other countries, which could potentially be made available under an FDA investigational new drug (IND) application. With remarkable cooperation from several companies and from other regulatory agencies (including the Paul Ehrlich Institute, Germany; Therapeutic Goods Administration, Australia; Swiss Medic and Health Canada) FDA immediately sent inspectors and scientists to the manufacturing facilities of potential IND sponsors to evaluate their manufacturing processes. Coupled with these efforts, we also reviewed a large volume of manufacturing and clinical data, all within a few weeks. These efforts resulted in INDs that would have permitted the use of approximately four million doses from GlaxoSmithKline (GSK) and one million doses from Berna Biotech, had they been needed. HHS and FDA's coordinated interactions with these and other influenza vaccine manufacturers and regulatory agencies also provided valuable information and strengthened relationships that helped stimulate interest by

additional influenza vaccine manufacturers to pursue U.S. licensure. This is one constructive outcome of the challenges we faced this past flu season. I am very proud of the efforts and accomplishments of more than 50 FDA employees, from multiple offices, as well as our HHS and CDC colleagues, working collaboratively for long hours to help meet this public health challenge.

Efforts to Enhance Antiviral and Pneumococcal Vaccine Supplies

Following the loss of the Chiron vaccine, FDA also contacted manufacturers worldwide in an effort to identify additional supplies of antiviral medications that could be used, if needed, for treatment of millions of influenza cases and for prevention in high-risk individuals in epidemic settings.

Serious morbidity and mortality from influenza is often due to the complication of bacterial pneumonia. In particular, pneumococcal pneumonia is one of the most common serious complications of influenza in high-risk individuals. This complication is preventable through use of an inexpensive, yet underutilized, pneumococcal vaccine. The influenza vaccine shortage provided an impetus to increase the availability of vaccine against pneumonia. In cooperation with HHS, Merck & Company tripled its production of its pneumococcal polysaccharide vaccine from 6 million to more than 17 million doses. The beneficial effects of pneumococcal vaccine last for five to ten years, and CDC and other public health agencies strongly encourage its use.

PLANS FOR 2005 AND FUTURE YEARS

At the same time that we have addressed the past year's shortage by facilitating the availability of additional vaccine, antivirals, and pneumococcal vaccine, we are doing everything we can to help improve supply for future years. We are applying a dual-track strategy.

First, the most important single factor that will affect the status of the U.S. influenza vaccine supply for the coming year will be whether Chiron can correct its manufacturing problems at the Liverpool facility and supply vaccine for the U.S. market. To succeed, Chiron must implement extensive improvements needed to satisfy both FDA and the U.K. regulatory authority. We have come a long way since October 5, 2004, when MHRA could not legally communicate with FDA about its pending enforcement action.

After MHRA's suspension of Chiron's license to manufacture influenza virus vaccine at the Liverpool facility, Chiron gave MHRA and FDA permission to discuss information that could not otherwise be shared. This arrangement allowed free exchange of information as the company initiated efforts to address the problems at Liverpool. Then, on February 14, 2005, FDA signed a general information-sharing agreement with MHRA that, among other things, permits advance communication on important issues and not limited to Chiron's influenza vaccines. Chiron developed an extremely comprehensive remediation plan which has been undergoing implementation during recent months. FDA and

MHRA reviewed and provided extensive input on this plan and the Agency continues to provide extensive feedback to both Chiron and MHRA.

FDA and MHRA are also working together and actively communicating on inspectional activities. For example, FDA accompanied MHRA on inspections of the Chiron Liverpool facility in December 2004 and February 2005, and has had very frequent interactions with both Chiron and MHRA concerning implementation of the remediation plan and start up of manufacturing activities. As a result of progress in the Liverpool facility, MHRA lifted its license suspension on March 2, 2005, which has allowed Chiron to proceed with manufacturing plans. FDA is continuing to interact intensively with both MHRA and Chiron as the company further institutes its remediation plan and begins to gear up for manufacturing.

FDA will continue to coordinate with and accompany MHRA on future inspections – one of which is currently in the planning stage. FDA will continue to provide MHRA and Chiron with feedback and information. Once Chiron has implemented all key remediation measures and critical stages of manufacturing are in full swing (likely in late Spring or early Summer), FDA will conduct a complete and comprehensive inspection of Chiron's Liverpool facility to verify that Chiron has adequately addressed its problems. Our continuing interactions with Chiron indicate the significant progress that has been made in a short period of time, but it is also clear that full scale manufacturing and all its associated

challenges remain and will require continuing intensive efforts that will need to succeed under very tight time frames. Only after passing MHRA and FDA inspections will Chiron be able to provide vaccine for the U.S. market. Chiron's vaccine will have to meet all FDA-required standards, including sterility and other safety testing, prior to distribution to the public. While it is too early to predict the outcome of Chiron's remediation activities, Chiron is making continuing progress toward its goal of being able to supply vaccine for the US market for the upcoming season.

While working hard to facilitate Chiron's efforts to correct its manufacturing problems, FDA is also working on a second track to improve preparedness for this and future influenza seasons and facilitate greater overall capacity and diversification of the U.S. influenza vaccine supply. It is important to recognize, however, that demand for vaccine and other economic factors are, and will, remain the primary factors that determine 1) whether a manufacturer will seek and maintain licensure, 2) the strength of the manufacturing infrastructure in the U.S., and 3) the amount of vaccine that manufacturers produce for the U.S. market. These factors also apply to other vaccines and the U.S. vaccine supply infrastructure in general. CDC and FDA are working to encourage extending vaccination throughout the flu season, including January and February. If such demand exists, manufacturers can increase total doses available by producing vaccine that becomes available during these months. Because influenza cases usually continue or peak well after the November-December time period when

most people seek immunization, continuing vaccination is beneficial to recipients and should be encouraged.

MedImmune is performing studies that, if successful, may support future use of its vaccine in additional age groups. MedImmune has also stated that, if successful, it should be able to produce additional vaccine to support those needs. Sanofi pasteur has indicated that it has the capability to produce the same or more doses of Fluzone for the 2005-2006 influenza season as it did in 2004-2005. Greater influenza vaccine production capacity and an increase in vaccination rates are also critical for improving our preparedness for a global pandemic. In the event of a pandemic, we would need the capacity to rapidly produce a new vaccine and make it available to all who need it.

While greater production by currently-licensed manufacturers will enable us to meet some of these needs, recent events highlight the potential benefits of having more U.S.-licensed manufacturers. In recognition of this, FDA has been doing everything possible to stimulate interested foreign-licensed manufacturers to provide or, where needed, develop the safety and effectiveness data required for U.S. licensure. FDA has interacted constructively with several interested firms in this regard. FDA has informed manufacturers that it is willing to consider new approaches to influenza vaccine licensing, such as accelerated approval based on likely surrogate markers (e.g. the degree of antibody response to the vaccine), followed by post-licensure clinical effectiveness evaluation. The

National Institute of Allergy and Infectious Diseases (NIAID) supported clinical studies of GSK's influenza vaccine. Thanks in part to that research, GSK has stated that it expects to submit the needed data to FDA to seek accelerated approval of its influenza vaccine for the U.S. market in the near future. GSK has stated that if its vaccine is licensed, it expects to be able to supply 10 million doses of vaccine in time for the 2005-6 season. ID Biomedical of Canada has also indicated interest in seeking accelerated approval for its influenza vaccine. It has stated that it expects to complete needed studies and submit a license application in 2006 and that, if licensed, vaccine would potentially be available in time for the 2006-7 season.

So, in preparation for the upcoming influenza season, we are continuing to do everything we can to facilitate both Chiron's remediation and GSK's licensure efforts so that these vaccines can potentially be available to help meet the 2005-6 flu season's needs. In either case, potential difficulties should become apparent during the summer. If it becomes necessary to obtain additional vaccine for use under an IND, the experience and relationships built this year through reviewing and obtaining vaccines licensed by other regulatory authorities will be helpful.

OTHER IMPORTANT ACTIVITIES

We have challenged ourselves to identify other lessons learned from this past year's influenza season and to examine how we can use our recent experience

to help prevent similar problems in the future. For example, as I previously mentioned, we have identified the need to allow free flow of information between FDA and our international regulatory counterparts, and vice versa. We committed to do so and have now completed confidentiality commitments that allow such information sharing with regulatory agencies in the UK, Australia, Canada, the European Commission, Japan, Mexico, Switzerland, Singapore, and South Africa. We are also in final negotiations on an agreement with New Zealand. We are undertaking discussions with several additional European countries where vaccine manufacturing important to U.S. public health takes place. In addition, we are continuing to inventory foreign manufacturing to identify any additional information-sharing needs. We also plan to seek agreements with other national regulatory authorities where necessary. These commitments will help assure that legal barriers do not inhibit critical communication between these agencies and FDA.

As in past years, FDA will work closely with CDC, WHO and others to develop materials for standardization and evaluation of influenza vaccine for the 2005-2006 flu season. FDA will continue to identify and evaluate influenza virus strains suitable for manufacturing purposes and provide to manufacturers the high growth reassortant viruses they need to help to facilitate efficient, timely and adequate production of vaccine.

Recent events highlight the importance of FDA's technical support for the U.S. and global vaccine manufacturing infrastructure and the need for manufacturers to invest in more efficient, reliable and modern methods for producing influenza vaccine. With adequate supply and widespread immunization, we will be more likely to meet the challenge of annual influenza epidemics and future pandemics.

CBER has also initiated a vulnerability analysis of foreign manufacturing of U.S. licensed products that are critical to U.S. public health. This analysis will include other vaccines and help to identify areas where consideration of actions to support supply may be needed, such as stockpiling or seeking additional licensed manufacturers. In addition, in the hope that more vaccines can be licensed and available to multiple regions of the world, FDA has been working with our foreign regulatory counterparts and with manufacturers to enhance international communication with the goal of more efficient product development. We are also encouraging development of scientific and regulatory standards for safety, potency and effectiveness that will help achieve these goals. FDA serves as a designated Collaborating Center of the World Health Organization (WHO), and we work closely with our sister agencies at HHS and WHO on pandemic preparedness and responding to other emerging infectious diseases.

Under FDA's Critical Path initiative, we are working collaboratively with HHS agencies and the private sector to facilitate the rapid development, evaluation and availability of medical products and related manufacturing, safety and

effectiveness standards. The rapid development and implementation of a West Nile Virus screening test for the blood supply provides a good example of the effectiveness of this type of a collaborative public-private approach to meet the threat of emerging infections.

To help manufacturers overcome challenges such as the problems Chiron is experiencing, FDA, under its current Good Manufacturing Practice for the 21st Century initiative, is working with industry to encourage the use of advanced technologies, quality systems and risk-based approaches that build quality into the manufacturing process. FDA is also using the same quality systems and risk-based approaches to modernize its manufacturing-related regulatory responsibilities. Recognizing that clarity and quality in vaccine GMPs is of increasing importance, CBER has planned increasing outreach in this area for the coming months, including international workshops and meetings.

The experiences of the past six months have taught us important lessons about manufacturing and inspectional activities with respect to influenza vaccine. The annual changes in the flu vaccine and the increased dependence on a smaller number of manufacturers highlight the risks of unexpected manufacturing difficulties. For these reasons, in 2005 and the future, we plan to inspect influenza vaccine manufacturers annually. Further, while FDA has always interacted extensively with influenza vaccine manufacturers throughout the vaccine production cycle, we plan additional interactions, including foreign

regulatory agencies where appropriate, based on findings or events that raise concerns.

PANDEMIC PREPAREDNESS

HHS is working to help transform the influenza marketplace and reinvigorate the influenza vaccine infrastructure by investing in promising new technologies, securing additional licensed vaccines and medicines and preparing stronger response plans and capacity. Furthermore, the lessons we have learned and insights gained from recent experiences with influenza vaccine are critical in preparing for an influenza pandemic. This is something that FDA and others in the public health community are very concerned about, given the eventual likelihood of a pandemic and the recent outbreaks of avian influenza in Asia. More widespread vaccination during periods between pandemics not only has direct health benefits but also will increase vaccine production capacity and help America and the global community better prepare for an influenza pandemic.

As part of HHS' efforts to support pandemic preparedness, NIAID contracted for the production of pilot lots of potential pandemic vaccines from two licensed U.S. manufacturers. HHS contracted for the production of two million doses of vaccine against H5N1 avian flu, the influenza type of current concern in Southeast Asia. NIAID recently initiated critical clinical studies of the first H5N1 vaccine under INDs that FDA oversees, and both agencies will be working together to evaluate the results. While much work remains, these steps to

produce and evaluate pandemic influenza vaccines are a critical component of our preparedness efforts. They will inform us about the needed dosing and schedule of pandemic vaccine and help pave the way for evaluation and potential licensure and broader use of a vaccine against avian flu if needed.

In addition, NIH and FDA support studies to develop vaccine strategies that could lead to longer-lived immunity and the production of an immune response that could potentially allow one year's vaccine to better provide immunity for multiple flu seasons. FDA is actively engaged with sponsors and manufacturers interested in developing new technologies for influenza vaccine manufacture, including cell-culture based and recombinant vaccines. FDA has extensive experience in overseeing the development and licensure of cell-culture based and recombinant vaccines including those for prevention of other infectious diseases, such as chicken pox, polio, rubella, and hepatitis A and B.

FDA's goal is to support a process to produce pandemic influenza vaccine in the shortest amount of time possible and protect the largest number of people, using a vaccine that is safe, effective and easy to deliver. The full details of the draft Pandemic Influenza Preparedness and Response Plan are located on the HHS website at: <http://www.dhhs.gov/nvpo/pandemicplan/annex5.pdf>. Through all these efforts, and with enhanced global surveillance by CDC and its partners, we have the unique opportunity to effectively intervene and potentially blunt a global pandemic, should one occur.

CONCLUSION

HHS has proposed spending of \$439 million Department-wide on influenza related activities in the FY 2006 President's Budget. This amount is an increase of \$397 million over the FY 2001 level of \$42 million, and represents the Administration's commitment to addressing this important public health concern.

Although we may never completely prevent influenza outbreaks, we can greatly decrease our vulnerability and provide protection against influenza with a robust vaccine supply supplemented by effective antivirals. FDA recognizes the need to continue to work with multiple partners, including manufacturers, to increase supply and to support progress toward more modern, dependable methods of production. All of the steps we have discussed will not only help protect Americans from flu every year but will help prepare us for future influenza seasons or in the event that a pandemic strikes. We welcome the opportunity to work with Congress to accomplish these important public health goals.

Once again, thank you for inviting me to testify on this very important issue. I am happy to respond to your questions.