



FDA Pandemic Influenza Preparedness Strategic Plan

United States Department of Health and Human Services
Food and Drug Administration
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I. Executive Summary

In general, influenza viruses tend to be species-specific, such that an influenza virus that affects birds usually does not affect people. However, exceptions do occur. In 1997, a highly pathogenic avian influenza virus (belonging to a subtype known as H5N1¹) appeared to cross the species barrier and result in severe illness and death in humans in Asia. Since then, highly pathogenic avian influenza has spread to bird populations in other areas within and outside Asia and also has caused illness and death among humans in a growing number of countries. Human cases of H5N1 avian influenza (AI, also known informally as "bird flu") appear to be the primary result of close or direct contact with infected birds, but there is concern that the virus could mutate into a form that is easily transmitted between humans. If efficient and sustained human-to-human transmission of a new influenza subtype occurs, experts believe the result would be an influenza pandemic because humans would not have any previous immunity to the virus.

Therefore, to prepare for an influenza pandemic, the Food and Drug Administration (FDA) developed this FDA Pandemic Influenza Preparedness Strategic Plan. The FDA Pandemic Influenza Preparedness Strategic Plan coordinates with and complements the President's National Strategy for Pandemic Influenza, the Implementation Plan for the National Strategy for Pandemic Influenza, and the Department of Health and Human Service's (HHS's) Pandemic Influenza Plan and the HHS Pandemic Influenza Implementation Plan – Part 1 (discussed in parts III.A, III.B, and III.C).

Part II, Strategic Plan Overview, describes the formation of an FDA Task Force to prepare the FDA Pandemic Influenza Preparedness Strategic Plan, the principles that shaped or guided the plan's development, and recurring themes. For example, coordination among Federal, State, local, and tribal governments and private sector parties and communication are two important principles in preparing for and ultimately minimizing the effects of an influenza pandemic. Other key principles shaping the plan include the following:

- Domestic vaccine production capacity sufficient to provide vaccines for the entire United States population is critical, as is development of a vaccine against each circulating influenza virus with pandemic potential and, ideally, development of a vaccine that confers cross-protective immunity;
- Development of anti-viral drug products and devices is important in preparing for, and responding to, an influenza pandemic; and
- Availability of improved point-of-care diagnostic devices to detect and also differentiate between seasonal influenza viruses and novel influenza A viruses having pandemic potential. This differentiation could be critical for effective patient management and pandemic influenza preparedness and response. Healthcare providers will need guidance to use point-of-care tests effectively and to use results in patient management, both in pre-pandemic and pandemic influenza phases.

Facilitating the development of vaccines, anti-viral drug products, and devices before an influenza pandemic occurs means we must take a proactive role in working with manufacturers, academia, and others to identify promising new therapies and to

determine how we might ensure that our review of such products is as efficient as possible. It also means communication and teamwork between public and private parties will be important so all parties are aware of new developments and can use their resources effectively.

Part III, Background, provides basic information about influenza viruses, the National Strategy for Pandemic Influenza, and the HHS Pandemic Influenza Plan. The former plan coordinates pandemic influenza preparedness and response at all government levels, the private sector, individual citizens, and international entities.² The latter plan is a "blueprint" for pandemic influenza preparedness and response planning within HHS and also provides guidance on specific aspects of pandemic influenza planning and response for State and local preparedness plans.³ These two plans and their associated implementation plans provide a framework for the FDA Pandemic Influenza Preparedness Strategic Plan.

Part IV, FDA Roles and Responsibilities, describes the FDA centers and offices that will have important roles in preparing for, and responding to, an influenza pandemic. It also describes the subgroups within the FDA Task Force and their main responsibilities. In brief:

- The Center for Biologics Evaluation and Research leads the Vaccine and Other Biologics Development, Production, and Regulatory Review Subgroup;
- The Center for Drug Evaluation and Research leads the Anti-viral Drug Development, Production, and Regulatory Review Subgroup;
- The Center for Devices and Radiological Health leads the Device Development, Production, and Regulatory Review Subgroup;
- The Center for Food Safety and Applied Nutrition and the Center for Veterinary Medicine lead the Food and Feed Safety Subgroup;
- The Office of Crisis Management and the Office of External Relations lead the Emergency Preparedness, Response, and Communication Subgroup; and
- The Office of Regulatory Affairs leads the Enforcement Subgroup.

Additionally, the Office of International Programs manages FDA's international activities and interactions with the Office of the Secretary, HHS and advises the centers and offices regarding our international pandemic influenza preparedness activities.

Part V, FDA Accomplishments, describes some recent actions we have taken to prepare for a possible influenza pandemic.

Part VI, FDA Objectives and Actions, lists various pandemic influenza preparedness activities that are or will be critical to the development, review, and approval of vaccines, anti-viral drug products, and devices or to safeguarding food and animal feed. It also lists activities for protecting Americans against fraudulent or counterfeit pandemic influenza products. This part describes our objectives, the actions to be taken to further those objectives, and "deliverables" (the expected result or end-product for a particular action).

Part VII, Tables of FDA Objectives and Actions, summarizes our intended actions, deliverables, and timeframes in relation to our larger pandemic influenza preparedness objectives. We have organized the tables according to the individual subgroups within the FDA Task Force on Pandemic Influenza Preparedness. (We discuss the FDA Task Force on Pandemic Influenza Preparedness in the next section.)

II. Strategic Plan Overview

Pandemic influenza is a significant public health threat to our nation and to the world. Across the globe, officials are developing

plans to prepare for, and respond to, the next influenza pandemic. Though no influenza pandemic has struck the United States in decades, scientists are concerned that the highly pathogenic avian influenza strain (H5N1) currently circulating in wild and domestic birds in Asia, Europe, the Middle East, and Africa could mutate into a form capable of efficient and sustained human-to-human transmission which could result in a global outbreak (a pandemic). Preparedness planning is imperative to lessen the impact of such a pandemic. To this end, on November 1, 2005, the President issued a National Strategy for Pandemic Influenza that called for comprehensive and coordinated pandemic preparedness planning at all levels of government and the private sector. On November 2, 2005, the Secretary of Health and Human Services, Michael O. Leavitt, released the HHS Pandemic Influenza Plan which provides a blueprint for all HHS pandemic influenza preparedness planning and response activities.

To increase the Nation's preparedness for an influenza pandemic, in November 2005, the (then Acting) Commissioner for Food and Drugs, Andrew von Eschenbach, M.D., established an FDA Task Force on Pandemic Influenza Preparedness to set into operation FDA's participation in the President's National Strategy for Pandemic Influenza and the HHS Pandemic Influenza Plan. The FDA Task Force members include representatives from the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), Center for Food Safety and Applied Nutrition (CFSAN), Center for Veterinary Medicine (CVM), National Center for Toxicological Research (NCTR), Office of Regulatory Affairs (ORA), Office of the General Counsel's Food and Drug Division (OGC), Office of Counterterrorism Policy and Planning, Office of Crisis Management, Office of International Programs, Office of Pediatric Therapeutics, Office of Policy and Planning, the Office of Science and Health Coordination, and the Office of External Relations.

The FDA Task Force's key charges were to:

- Develop a comprehensive action plan to accelerate the development, production, and regulatory review of vaccines, anti-viral drug products, diagnostics, personal protective equipment, and other devices as pandemic countermeasures;
- Develop a comprehensive food and feed security strategy;
- Protect the safety and security of regulated medical products;
- Enhance emergency preparedness and response capabilities; and
- Pursue enforcement actions to curtail production, shipment, trade, and use of fraudulent or counterfeit products.

The Task Force also was charged with developing an implementation strategy for the FDA Pandemic Influenza Preparedness Strategic Plan.

This FDA Pandemic Influenza Preparedness Strategic Plan reflects the diligent work of the FDA Task Force on Pandemic Influenza Preparedness and its subgroups and will serve as the basis for the implementation strategy. We expect to update the FDA Pandemic Influenza Preparedness Strategic Plan periodically as circumstances warrant.

The following principles guided our development of this plan:

- Preparedness will require coordination among Federal departments and agencies, State, local, and tribal governments, foreign governments, and private sector parties (such as industry, healthcare professionals, and academia).
- Communication is essential to minimizing the health effects of an influenza outbreak and for preparing for such an outbreak.
- Domestic vaccine production capacity sufficient to provide vaccines for the entire United States population is critical, as is the development of a vaccine against each circulating influenza virus with pandemic potential and, ideally, the development of a vaccine that confers cross-protective immunity.
- Development of anti-viral drug products, other biologic products, and devices is important in preparing for, and responding to, an influenza outbreak.
- Protection of human food and animal feed will include identifying food and feed at risk of AI contamination and identifying

- methods to inactivate influenza viruses.
- Protecting consumers from fraudulent or counterfeit products is also important in preparing for an influenza outbreak.
- Ensuring that our workforce has appropriate administrative and technological support and the best available public health information to remain effective throughout a pandemic influenza period is necessary.

These principles are similar to or complement those used in the HHS Pandemic Influenza Plan.

Consistent with the FDA Task Force's charges and guiding principles, the FDA Pandemic Influenza Preparedness Strategic Plan has several recurring themes. For example, to accelerate product development, we have to be proactive in working and communicating with industry, academia, and others, including sister agencies, such as the Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH), within HHS to determine which approaches will be the most efficient and the most effective. In many cases, this means we will assume a leadership role in identifying important issues and communicating about scientific and regulatory developments. These communications can take many different forms and range from hosting or participating in meetings and conferences to posting information on our Web site.

In all cases, teamwork and cooperation between FDA's centers and offices, between HHS agencies, between Federal, State, local, and tribal governments, or between the United States and other countries or international organizations (such as the World Health Organization (WHO), the Food and Agriculture Organization, and the World Organisation for Animal Health (better known as the OIE)) are essential for a better understanding of potential pandemic influenza issues and better solutions.

In addition, active involvement by all stakeholders is critical for an effective national response. For example, while we can facilitate product development and regulatory review and help ensure that products are available, other parties (such as academia, industry, and other government agencies) must fund and conduct the research (including clinical testing) necessary to invent a product, investigate its safety and effectiveness, and, ultimately, manufacture the product.

III. Background

A. The Pandemic Influenza Threat

Influenza A viruses have the capacity to infect many different animal hosts. The influenza A viruses typically seen in one animal species may sometimes infect and cause illness in another species. The potential for genetic mixing of different influenza A viruses within human or animal hosts, or the spontaneous mutation of individual viruses, creates the possibility that a new influenza A virus could develop. A new influenza A virus could be highly infective and easily transmissible from person to person, thereby creating a pandemic. If a pandemic influenza virus were to develop, 25 percent to 35 percent of the United States population could become ill, and many infected individuals could die.⁴

Currently, the H5N1⁵ influenza A virus is spreading in domestic and migratory birds in Asia, Europe, the Middle East, and Africa, and has infected humans primarily in Asia and the Middle East. The virus is endemic in many bird species in Asia, so eradication is unlikely.⁶ As of March 8, 2007, there have been 277 confirmed human cases reported to the WHO, and 168 of those infected have died.⁷ To plan and prepare for possible pandemic influenza, the Federal government has developed strategic plans with associated implementation plans, two of which are discussed below. FDA's Pandemic Influenza Preparedness Strategic Plan coordinates with and complements the President's National Strategy for Pandemic Influenza and the HHS Pandemic Influenza Plan and their associated implementation plans.

B. National Strategy for Pandemic Influenza

In November 2005, President George W. Bush released the National Strategy for Pandemic Influenza.⁸ This strategic plan

leverages and coordinates pandemic influenza preparedness and response at all levels of government, the private sector, individual citizens, and international entities. The National Strategy is intended to: (1) stop, slow, or otherwise limit the spread of a pandemic to the United States; (2) limit the domestic spread of a pandemic, and mitigate disease, suffering and death; and (3) sustain infrastructure and mitigate impact to the economy and the functioning of society. The pillars of the National Strategy are: (1) preparedness and communication; (2) surveillance and detection; and (3) response and containment. The National Strategy provides a framework for the FDA Pandemic Influenza Preparedness Strategic Plan and guides our planning and actions.

In May 2006, the President issued the Implementation Plan for the National Strategy for Pandemic Influenza.⁹ The implementation plan translates the National Strategy into over 300 actions for Federal departments and agencies and establishes clear expectations for State and local governments and non-federal entities; actions involving regulatory oversight of countermeasures (such as anti-viral drugs, vaccines, diagnostic devices, and personal protective equipment) are FDA's responsibility.

C. HHS Pandemic Influenza Plan

Secretary of Health and Human Services Michael O. Leavitt released the HHS Pandemic Influenza Plan on November 2, 2005.¹⁰ This plan consists of two parts: the HHS Strategic Plan, and a Public Health Guidance for State and Local Partners. The HHS Strategic Plan outlines key planning assumptions that we have adopted for our plan. In addition, the HHS Strategic Plan identifies necessary capabilities and pandemic planning and response actions, sorted by the WHO's pandemic phases. The plan assigns lead roles and responsibilities for response actions to specific HHS agencies and offices. We use the HHS Strategic Plan to identify and guide actions where we are the designated lead. Key pandemic response elements identified by HHS, such as surveillance, investigation, and protective public health measures; vaccine, anti-viral drug, and device products; healthcare and emergency response; and communication and public outreach are all actions that we addressed while developing the FDA Pandemic Influenza Preparedness Strategic Plan.

In December 2006, HHS issued the "HHS Implementation Plan."¹¹ The HHS Implementation Plan implements the strategy laid out in HHS Strategic Plan and the Public Health Guidance for State and Local Partners and itemizes the specific roles and responsibilities of HHS operational and staff divisions in planning for and responding to an influenza pandemic. The document identifies specific steps that operationalize and implement the actions and expectations outlined for HHS in the National Strategy. In addition, it identifies additional actions for successfully accomplishing the activities laid out in both the National Strategy and the HHS Strategic Plan. The HHS Implementation Plan is divided into two parts. The first part discusses HHS-wide issues, such as international activities, international and domestic surveillance, public health interventions, medical response, vaccines, anti-viral drugs, diagnostic devices, personal protective equipment (PPE), communications, and State and local preparedness. These issues require coordination of efforts across HHS operational divisions. The first part details the specific steps needed to meet the challenges of an influenza pandemic response and the critical capabilities as identified in both the National Strategy and the HHS Strategic Plan, and, as with those plans, guided our own planning and actions.

The second part of the HHS Implementation Plan includes detailed continuity of operations plans that ensure that the essential functions of each HHS operating division are identified and maintained in the presence of an expected decrease in staffing levels during an influenza pandemic.

IV. FDA Roles and Responsibilities

We are responsible for protecting the public health by helping to ensure the safety and effectiveness of human and animal drugs, human biological products, and devices, and the safety of our nation's food supply, cosmetics, and radiation-emitting products. We also advance the public health by helping to speed the availability of beneficial, innovative medical products and by helping the public get the accurate, science-based information it needs to use medical products and foods to improve health. Additionally, recognizing the global nature of public health issues, we collaborate with foreign counterpart regulatory agencies and international organizations in carrying out our mission.

We play a vital role in the Nation's preparedness for, and potential response to, an influenza pandemic. This FDA Pandemic Influenza Preparedness Strategic Plan provides a solid foundation for a cross-cutting initiative involving many of our centers and offices. The principal centers and offices, and their roles, are as follows:

- The Center for Biologics Evaluation and Research (CBER) leads the Task Force's Vaccine and Other Biologics Development, Production, and Regulatory Review Subgroup and is responsible for:
 - Facilitating the development, production and regulatory review of biological products;
 - Interacting with Federal entities, such as other HHS components, and industry, the public, and other pandemic influenza preparedness entities, as appropriate, on vaccine development for influenza and pre-investigational new drug application (pre-IND), investigational new drug application (IND), emergency use authorization (EUA), or biologics license application (BLA) interactions;
 - Conducting post-market surveillance and enforcement activities relating to biological products;
 - Assisting and coordinating in the vaccine and other biologics effort with Federal entities, such as the HHS Office of the Assistant Secretary for Preparedness and Response, CDC, and NIH; and
 - Conducting related outreach to industry, foreign public health authorities, the public, and other stakeholders regarding vaccines and other biologics.

Within CBER, the Office of the Director, the Office of Vaccines Research and Review, the Office of Compliance and Biologics Quality, the Office of Biostatistics and Epidemiology, the Office of Blood Research and Review, the Office of Cell, Tissue, and Gene Therapies, the Office of Communication, Training and Manufacturers Assistance, the Office of Management, and the Office of Information Technology are responsible for the objectives outlined in this plan and work together to ensure that action items are addressed.

- The Center for Drug Evaluation and Research (CDER) leads the Task Force's Anti-Viral Drug Development, Production, and Regulatory Review Subgroup and is responsible for:
 - Facilitating the development and production of anti-viral drug products as exemplified in the regulatory review of anti-viral drug products;
 - Conducting post-marketing surveillance and enforcement activities relating to anti-viral drug products;
 - Interacting with Federal entities, such as other HHS components, industry, the public, and other pandemic influenza preparedness entities, as appropriate on anti-viral drug development for influenza and pre-IND, IND, EUAs, or new drug application (NDA) interactions;
 - Working with the Department of Defense (DOD) and FDA Shelf Life Extension Program (SLEP) and the HHS-managed Strategic National Stockpile (SNS) to facilitate understanding of issues related to stockpile-specific packaging and labeling of anti-viral drug products; and
 - Maintaining, through the Drug Shortage Group, the Critical Products Program database to facilitate monitoring and addressing supply and shortage issues for anti-viral drug products.
- The Center for Devices and Radiological Health (CDRH) leads the Task Force's Device Development, Production, and Regulatory Review Subgroup and is responsible for:
 - Facilitating device development, regulatory review, and production of diagnostic devices, personal protective equipment (PPE) (e.g., medical gloves, masks, and protective gowns), and other devices that may be needed during an influenza pandemic;
 - Conducting post-market surveillance to monitor the safety and effectiveness of influenza-related devices (including

- devices used for diagnosis, devices used to administer therapeutics, PPE, and devices used for supportive care);
 - Lending technical expertise and assistance to international efforts to prepare for a potential influenza pandemic;
 - Supporting efforts to ensure an adequate supply of influenza-related devices through cooperative interactions with manufacturers and distributors and coordination with the SNS to determine the adequacy of stocks and actions required to meet targeted amounts; and
 - Using an Emergency Shortages Data Collection System to identify and monitor supplies of certain devices that have the potential to be in short supply during influenza outbreaks.
- The Center for Food Safety and Applied Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM) share the lead roles in the Task Force's Food and Feed Safety Subgroup and are responsible for:
 - Coordinating food and feed safety activities and plans with Federal and State agencies, industry, and others;
 - Identifying foods and animal feeds that are at elevated risk of contamination and investigating the effectiveness of food and feed processing and preparation practices for inactivating influenza viruses;
 - Developing and disseminating recommendations on measures to prevent the spread of avian influenza (AI) virus via FDA-regulated foods and animal feeds;
 - Developing and evaluating analytical methods for identifying AI in foods; and
 - Prohibiting the extra-label use of influenza anti-viral drug products in animals when such use presents a risk to the public health.
- The Office of Crisis Management (OCM)/Office of Emergency Operations manages FDA's Emergency Operations Center (EOC) which will coordinate our emergency response activities for an influenza pandemic. As with all emergency response efforts, our EOC will serve as FDA's focal point for communication and coordination activities with the Secretary's Operations Center (SOC) and HHS agencies. The EOC uses the Incident Command Structure to maintain situational awareness, enhance collaboration and coordination, communicate critical information, and make and implement decisions during emergencies. OCM is developing an FDA Pandemic Influenza Response Plan which will further identify the EOC's role and responsibilities and its relationships with other FDA, HHS, and government entities during an influenza pandemic.
- OCM and the Office of External Relations (OER) share lead roles for the Task Force's Emergency Preparedness, Response, and Communication Subgroup and are responsible for:
 - Identifying roles and responsibilities for emergency preparedness, response, and internal and public communication, including the implementation of pandemic influenza preparedness exercises and training;
 - Ensuring continuity of business operations;
 - Developing and implementing risk communication plans; and
 - Interacting with HHS, and other Federal, State, local, and tribal entities during an influenza pandemic.
- The Office of Regulatory Affairs (ORA) leads the Task Force's Enforcement Subgroup. Compliance experts, including members from ORA and OGC, compose the Task Force's Enforcement Subgroup and are responsible for identifying enforcement roles and responsibilities, including the implementation of enforcement actions to curtail illegal activity, such as the marketing of counterfeit pandemic influenza anti-viral drug products, vaccines, devices, or other therapeutics. However, the Enforcement Subgroup will not address compliance issues associated with legally-marketed or legitimate pandemic influenza products; such issues will be considered by the vaccine, anti-viral and diagnostics subgroups (mentioned in the preceding bullets).
- The Office of International Programs (OIP) leads, manages, and coordinates FDA's international pandemic influenza preparedness activities and also coordinates our international activities with the Office of the Secretary, HHS, and other Federal departments, as necessary. OIP is responsible for:
 - Capacity building and technical cooperation initiatives with foreign agencies and international organizations; and

- Interactions on international issues with the HHS Office of Global Health Affairs (OGHA), Federal departments and agencies, and foreign agencies and international organizations.

Each Task Force Subgroup, or the Task Force as a whole, also may determine whether to establish a "rapid response team"¹² to achieve one or more of its identified actions or address a new and time-sensitive issue.

V. FDA Accomplishments

Even before we issued this plan, we had taken various steps to prepare for a possible influenza pandemic. These steps have included:

- Approving, on December 21, 2005, the use of Tamiflu (oseltamivir phosphate) for prevention (prophylaxis) of influenza in children 1 to 12 years of age. This new indication gives health care providers an option for preventing influenza in children following close contact with an infected individual. We also discussed at FDA's Pediatric Advisory Committee (PAC) on November 18, 2005, an Adverse Event safety update on Tamiflu. The advisory committee provided a public forum to discuss the safety of Tamiflu use in children as part of a routine drug safety update required by the "Best Pharmaceuticals for Children Act." We continued to monitor adverse event reports and then worked with the manufacturer to update the labeling on November 13, 2006 with regard to possible side effects, particularly in children, and to include instructions that pharmacists could use to prepare a suspension from Tamiflu capsules during a public health emergency if the marketed oral suspension was not available. An update on the adverse event labeling also was provided at the annual PAC meeting on November 16, 2006. Throughout 2006, we also worked with the manufacturer to address various manufacturing and shelf life issues.
- Approving, on March 29, 2006, the use of Relenza (zanamivir for inhalation) for prevention (prophylaxis) of influenza in adults and children 5 years of age and older. This new indication provides an additional option for health care providers to consider in the prevention of influenza.
- Clearing, on February 3, 2006, CDC's Influenza A/H5 (Asian lineage) Virus Real-Time RT-PCR¹³ Primer and Probe Set. Testing with these reagents will help diagnose influenza in patients who are infected with these specific viruses (influenza A/H5 Asian lineage) and provide epidemiological information for surveillance purposes. The test provides preliminary results on suspected H5 influenza samples within four hours once a sample arrives at the lab and testing begins. Previous testing technology would require at least two to three days before providing results.
- In connection with the activity described immediately above, in the *Federal Register* of March 22, 2006, we issued a classification final rule (71 FR 14377) and a special controls guidance document (71 FR 14534) related to our classification of the new Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set. Under the special controls applicable to this classification, the distribution of these devices is limited to labs with experienced personnel having training in standardized molecular diagnostic techniques and expertise in viral diagnosis and appropriate biosafety equipment and containment. These documents provide clear guidance and recommendations to aid manufacturers in developing new avian flu in vitro diagnostics, and help assure the continued safety and effectiveness of these tests.
- Issuing a final rule to prohibit the extra-label use of human influenza anti-viral drug products in the adamantane and neuraminidase inhibitor drug classes in chickens, turkeys, and ducks. We took this measure to help preserve the effectiveness of these drugs for treating or preventing influenza infection in humans. The final rule appeared in the *Federal Register* on March 22, 2006 (71 FR 14374).
- Issuing two draft guidance documents on March 2, 2006, pertaining to seasonal and pandemic influenza vaccines. These guidance documents will help manufacturers in the development and evaluation of new vaccines for seasonal and pandemic influenza and, as a result, help address the increased demand for influenza vaccine. The guidance documents also help support and define steps needed for development and evaluation of vaccines using new technologies (such as cell culture and recombinant manufacturing) and potential approaches to stretching limited pandemic influenza vaccine supplies (such as with the use of ingredients added to a vaccine to improve the immune response it produces, known as adjuvants and different vaccine delivery methods). They are titled, "Draft Guidance for Industry: Clinical Data Needed to Support the Licensure of

Trivalent Inactivated Influenza Vaccines" and "Draft Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines." The guidance documents are available on our Web site at www.fda.gov/cber/gdlns/trifluvac.htm and at www.fda.gov/cber/gdlns/panfluvac.pdf respectively.

- Issuing a guidance document on April 10, 2006, pertaining to "In Vitro Diagnostic Devices to Detect Influenza A Viruses: Labeling and Regulatory Path." This guidance document addresses recommendations for fulfilling labeling requirements applicable to all *in vitro* diagnostic devices intended to generally detect influenza A (or A/B) virus directly from human specimens, with a particular emphasis on ensuring appropriate labeling for legally marketed influenza A (or A/B) test devices whose clearances are not based on data addressing performance with regard to novel influenza A viruses infecting humans (including H5N1). The guidance document is available at our Web site at www.fda.gov/cdrh/oivd/guidance/1594.html.
- Sending Warning Letters to several firms who had made unproven claims that their products would treat or prevent "avian flu" or other forms of influenza. We have issued over 50 Warning Letters and have taken enforcement actions concerning such products. For example, in cooperation with U.S. Customs and Border Protection, we recently intercepted products at the border that purported to be "generic" Tamiflu, but which, in fact, contained Vitamin C and other substances that are not approved to prevent or treat influenza. Although the products were similar in appearance to genuine Tamiflu, they offer no therapeutic benefit. In another recent case, we worked with the Federal Bureau of Investigation to arrest an individual in Texas who administered counterfeit influenza vaccine to employees attending a corporate-sponsored health fair. In June 2006, an individual was sentenced to 36 months in prison after a federal jury convicted him of smuggling foreign, unlicensed influenza vaccines into the United States and attempting to sell the illegal vaccines to hospitals. In January 2006, a Licensed Practical Nurse, who operated a series of unauthorized vaccine clinics, was sentenced to nine months in prison after pleading guilty to dispensing drugs without a valid prescription. The nurse admitted to diluting some of the vaccine with saline to increase the quantity of her supply. This dilution reduced the quality and effectiveness of the vaccine.
- Preparing, and later updating, a document on "Questions and Answers on Avian Influenza ('Bird Flu') and Food Safety." We first issued this document on March 29, 2004, and updated it on November 29, 2005 and again on March 21, 2006. The document addresses questions that the public may have regarding food safety.
- Organizing and participating in a meeting co-sponsored by the National Academy of Engineering and the Institute of Medicine on "Vaccine Production: Potential Engineering Approaches to a Pandemic," with HHS, WHO, the Department of State, academia, and industry. The meeting was held on April 10 through 11, 2006 at Case Western University in Cleveland, Ohio. The meeting's goals were to:
 - Identify challenges to manufacturing influenza vaccines, including rapid production for pandemic influenza;
 - Discuss specific approaches for increasing influenza vaccine production using both existing and "next generation" technologies;
 - Provide a venue where a "community" of interested academic and industrial engineers, government regulators, and other scientists and physicians can bring an engineering perspective to critical demand situations; and
 - Identify research opportunities for young researchers and others new to the field.
- Conducting or participating in various meetings regarding Current Good Manufacturing Practice (CGMP) for vaccines. These meetings occurred from August 2005 through August 2006 in the United States and in Europe. The goal of these meetings was to:
 - Communicate regulatory expectations and promote the use of robust quality systems;
 - Provide examples of CGMP problems seen in the vaccine industry and the consequences of those problems; and
 - Elicit meaningful dialogue with the industry and our foreign regulatory counterparts on CGMP issues for vaccines.

We plan to conduct or participate in additional meetings in 2007.

- Convening a meeting of FDA's Vaccines and Related Biological Products Advisory Committee on November 16, 2005, to discuss the use of Madin-Darby canine kidney (MDCK) cells for manufacturing influenza inactivated vaccine.¹⁴ As we are aggressively supporting multiple efforts to increase manufacturing capacity, using both new and existing technologies, this

meeting provided an opportunity to actively engage sponsors and manufacturers interested in developing new technologies for manufacturing influenza vaccines.

- Meeting with foreign regulatory authorities to develop strategies for harmonizing, where feasible, regulatory pathways to facilitate the development and production of pandemic influenza vaccines. An FDA delegation attended a meeting hosted by Health Canada and co-sponsored by FDA and the WHO in Ottawa, Ontario, Canada, on March 9 through 11, 2006. At the conclusion of the meeting, there was general agreement among the participants on the pathways and requirements for licensure of pandemic influenza vaccines. It was decided that the formation of working groups would be the best way to develop strategy and to outline a framework of globally consistent regulatory approaches based on the available science. Working groups established soon after developed draft consensus documents representing such an approach. At a second meeting hosted by FDA in June 2006 in Bethesda, Maryland, the documents were reviewed and may become available in 2007.
- Posting center- and commodity-specific information and advice related to pandemic influenza on FDA's Web site. For example, we have posted information on FDA-regulated PPE at <http://www.fda.gov/cdrh/ppe/index.html>. The Web site includes questions and answers on PPE and influenza outbreaks, including avian flu. It is intended to provide technical and regulatory information on masks, respirators, gloves, and gowns to individuals in health care and other occupational settings and to the general public.
- Issuing a draft guidance document on September 29, 2006, to provide important advice to manufacturers on using cell cultures to produce needed vaccines against infectious diseases, including vaccines to address emerging and pandemic influenza threats. The document, titled "Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases," is available at our Web site at www.fda.gov/cber/gdlns/vaccsubstrates.htm.
- Licensing, on October 5, 2006, FluLaval, an influenza vaccine to immunize people 18 years of age and older against the disease caused by strains of seasonal influenza virus. With this action, the United States now has five licensed influenza vaccine manufacturers. Having additional manufacturers will enhance the capacity to product more doses of influenza vaccine every year and will contribute to the nation's pandemic influenza preparedness.
- Conducting, in cooperation with the Vietnamese Department of Science and Training, a training workshop on good clinical practices. The workshop was held in Hanoi, Vietnam, on October 2 through 6, 2006. The workshop was in support of HHS's international efforts for pandemic influenza preparedness. The training is also viewed as the first formal activity pursuant to the HHS-Vietnam Ministry of Health (MOH) Agreement on Health and Sciences Cooperation signed by Secretary Leavitt and Minister Tran Thi Chien on July 26, 2006. The training included 30 participants from the MOH, medical administrators from institutions in Hanoi, Ho Chi Minh City, and Hue, and local industry. The training will better equip the Vietnamese to provide oversight to clinical trials of potential avian influenza vaccines and anti-viral drugs that are being tested in the country.

The objectives, actions, and deliverables discussed in part VI below build on our earlier efforts. They are also consistent with, or elaborate upon, various Federal actions described in the Implementation Plan for the National Strategy for Pandemic Influenza and the HHS Pandemic Influenza Implementation Plan – Part 1.

VI. FDA Objectives and Actions

In general, our Pandemic Influenza Preparedness Strategic Plan identifies various activities that are or will be critical to the development, review, and approval of products for diagnostic, therapeutic, preventive, or other uses, safeguarding food and feed, and protecting Americans from fraudulent or counterfeit products. Our plan also addresses information dissemination and the need for continuity of business operations if a pandemic occurs.

We discuss various agency actions in this section of the plan. For each major topic, we include:

- Our objectives,
- Actions to be taken to further those objectives, and

- "Deliverables" or the expected result or end-product of a particular action, and the timeframes for such "deliverables," resources permitting.

As noted earlier, the HHS Pandemic Influenza Plan identifies necessary capabilities and pandemic planning and response actions, sorted by the WHO's pandemic phases. WHO uses the phase system in its own WHO Global Influenza Preparedness Plan to inform the world about the seriousness of a particular threat and the need to launch progressively intense preparedness and response activities. The WHO phases are grouped into periods as follows: an "inter-pandemic period" where a virus exists in animals, but there are no human cases of disease; a "pandemic alert period;" and a "pandemic period." There are two phases within the inter-pandemic period; phase 1 is when there is low risk of human cases. Phase 2 is when there is a higher risk of human cases. In the "pandemic alert" period, the new virus is causing disease in humans. There are three phases within the pandemic alert period; phase 3 is when there is no or very limited human-to-human transmission, while phase 4 is when there is evidence of increased human-to-human transmission. Phase 5 is when there is evidence of significant human-to-human transmission. In the "pandemic" period, phase 6 occurs when there is "sustained transmission in general population."

While the WHO phase system informs the world about the global risk for an influenza pandemic and global response capabilities, the Implementation Plan for the National Strategy for Pandemic Influenza contains another framework for Federal government actions. The Implementation Plan for the National Strategy for Pandemic Influenza describes the Federal government approach to an influenza pandemic response by characterizing the stages of an outbreak in terms of the immediate and specific threat a pandemic influenza virus poses to the United States population. The stages are:

- Stage 0: New Domestic Animal Outbreak in At-Risk Country;
- Stage 1: Suspected Human Outbreak Overseas;
- Stage 2: Confirmed Human Outbreak Overseas;
- Stage 3: Widespread Human Outbreaks in Multiple Locations Overseas;
- Stage 4: First Human Case in North America;
- Stage 5: Spread throughout United States; and
- Stage 6: Recovery and Preparation for Subsequent Waves.¹⁵

Under the Implementation Plan for the National Strategy for Pandemic Influenza, the Federal government response at each stage is, itself, divided into objectives, immediate actions, policy decisions, and communications and outreach activities. According to the Implementation Plan for the National Strategy for Pandemic Influenza,

"Immediate Actions" reflect those agreed-upon measures that would be triggered as each landmark for increasing risk to the U.S. population was passed. "Policy Decisions" reflect issues that would have to be considered by the Federal Government at the time, in the context of the available information about the pandemic and the status of our response. Finally, "Communications and Outreach" describes the high-level objectives of the guidance that is provided to the public; institutions; State, local, and tribal authorities; and our international partners.¹⁶

For example, at Stage 0, the objectives are to: (1) Track outbreaks to control/resolution; (2) provide coordination mechanisms, logistical support, and technical guidance; and (3) monitor for recurrence of disease. The actions for Stage 0 are to: (1) "Initiate dialogue with FAO, other relevant international health organizations, and other international partners to ensure complete coordinated support (Department of State (DOS) and USDA);" (2) "initiate dialogue with affected nation through diplomatic, animal health, and human health channels to ascertain situation, offer scientific, technical, and, potentially, economic and trade assistance, and encourage full and open sharing of information (DOS, HHS, and USDA);" (3) "prepare to deploy rapid response team including influenza epidemiology, diagnostics, public-health management, and communications, as part of bilateral and multilateral teams to assess situation and requirements for successful animal disease eradication and human disease prevention effort (DOS, USDA, U.S. Agency for International Development (USAID), Department of Defense (DOD), and HHS);" (4) "prepare

to supply testing protocols and deploy reagents and equipment to support diagnostic requirements for both animal and human testing (USDA, HHS, DOD, and DHS);" and (5) "prepare to deploy animal disease response materiel, including PPE (USDA and USAID)." The policy decision for Stage 0 is "deployment of countermeasures to affected country as part of the U.S. contribution to an animal disease control and eradication effort."¹⁷

For more information regarding the Federal government's response stages and the components of each stage, we refer readers to the Implementation Plan for the National Strategy for Pandemic Influenza.

The WHO phases and their accompanying public health goals,¹⁸ and the corresponding Federal government response stages, are as follows:

WHO Phase	Overarching WHO Public Health Goal	Federal Government Response Stages
<p>Interpandemic period</p> <p>Phase 1 – No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk¹⁹ of human infection or disease is considered to be low.</p> <p>Phase 2 – No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk²⁰ of human disease.</p>	<p>Strengthen influenza pandemic preparedness at the global, regional, national and subnational levels.</p> <p>Minimize the risk of transmission to humans; detect and report such transmission rapidly if it occurs.</p>	<p>Stage 0 – New domestic animal outbreak in at-risk country</p>

WHO Phase	Overarching WHO Public Health Goal	Federal Government Response Stages
<p>Pandemic alert period</p> <p>Phase 3 – Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact.²¹</p> <p>Phase 4 – Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.²²</p>	<p>Ensure rapid characterization of the new virus subtype and early detection, notification, and response to additional cases.</p> <p>Contain the new virus within limited foci or delay spread to gain time to implement preparedness measures, including vaccine development.</p> <p>Maximize efforts to contain or delay spread, to possibly avert a pandemic, and to gain time to implement pandemic response measures.</p>	<p>Stage 0 - New domestic animal outbreak in at-risk country</p> <p>Stage 1 – Suspected human outbreak overseas</p> <p>Stage 2 - Confirmed human outbreak overseas</p>

<p>Phase 5 – Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).²³</p>		
<p>Pandemic period</p> <p>Phase 6 – Pandemic: increased transmission in general population.</p>	<p>Minimize the impact of the pandemic</p>	<p>Stage 3 – Widespread human outbreaks in multiple locations overseas Stage 4 – First human case in North America Stage 5 - Spread throughout the United States Stage 6 – Recovery and preparation for subsequent waves</p>

FDA's Pandemic Influenza Preparedness Strategic Plan does not link specific objectives or actions to the WHO phases because the majority of our objectives and actions span all six WHO phases. Nevertheless, we have described the WHO phases above because the HHS and WHO plans refer to the WHO phases and because FDA's Pandemic Influenza Preparedness Strategic Plan complements the HHS Pandemic Influenza Plan.

In the tables of FDA Objectives and Actions (Part VII of this document), we have cross-referenced our objectives and actions, where appropriate, to the Implementation Plan for the National Strategy for Pandemic Influenza. This will enable readers to understand how this plan fits within the Implementation Plan for the National Strategy for Pandemic Influenza, and subsequently the HHS Pandemic Influenza Implementation Plan – Part 1 which also references the National Strategy actions. However, this FDA Pandemic Influenza Preparedness Strategic Plan may contain additional details or activities that are narrower in scope than those in the national or HHS implementation plans.

A. Vaccine and Other Biologics Development, Production, and Regulatory Review

Vaccines are very effective in preventing viral diseases in humans, but vaccine development and production are complex processes. In very broad terms, vaccines use inactivated (killed) or live attenuated (weakened) bacteria or viruses that are identical or similar to those that cause a disease. Vaccines work by stimulating the body's immune system such that, when the disease-causing agent enters the body, the body's immune system recognizes the agent and mounts an immune response.

Seasonal influenza vaccine is unique in that its composition changes almost every year. Public health experts annually evaluate world-wide epidemiological data to determine the strains of the virus that manufacturers will use to make the influenza virus vaccine administered in the fall. Currently, seasonal influenza vaccines licensed in the United States are produced using fertile hen's eggs as part of a complex and exacting process. Companies and researchers are actively studying new manufacturing methods, such as cell-culture based and recombinant technologies, along with adjuvants²⁴ and other dose-sparing techniques.

For seasonal influenza, vaccines are the primary method for preventing and controlling influenza. Our experience with seasonal influenza vaccines has helped us devise regulatory policies and strategies for pandemic influenza vaccines. Because seasonal influenza vaccine manufacturers will likely produce pandemic influenza vaccines, increases in manufacturing capacity and improvements to existing processes directly impact our ability to produce pandemic influenza vaccines. We also are using

knowledge gained from past experience with counterterrorism products and with the 2004/2005 flu vaccine shortage to facilitate the regulatory review of new BLAs and supplements to existing applications for influenza vaccines.

Furthermore, to enhance preparedness and vaccine quality, we have increased our post-approval surveillance of influenza vaccine manufacturers by inspecting manufacturing facilities annually.

Vaccines would be an important part of an influenza pandemic response and, along with other FDA-regulated products, would help prevent transmission or spread of the pandemic influenza virus. Those other FDA-regulated products include anti-viral drugs, which might be used in selected situations, either to protect against influenza illness or to treat individuals who have contracted the virus. They also include medical devices, particularly diagnostic devices that would help confirm whether an individual had contracted the virus thus helping public health authorities decide how to treat individuals and to prevent further transmission.

Other products of biological origin also serve an important role in addressing an influenza pandemic. Blood, cell, and tissue products are critical in supporting health care and emergency response. We are working with other HHS components, other Federal departments and agencies, and blood and tissue organizations to enhance preparedness by focusing on safe and available blood, cell, and tissue products.

Objective VI.A.1: Facilitate vaccine development, production, and regulatory review.

Action VI.A.1.a: Assist efforts to increase manufacturing capacity and product diversity through meetings with vaccine manufacturers. The meetings will address issues such as facility design, non-clinical and clinical studies, and manufacturing.

Deliverables:

- Meetings with vaccine manufacturers to discuss design plans for vaccine facilities.
- Expedited review of BLAs and supplemental applications that could increase both the number of manufacturers and the overall supply of vaccine.

Timeframe:

- Initial meetings with manufacturers to provide guidance on vaccine facility design and commissioning began in 2004. Routine follow-up discussions occurred in fiscal year 2006 and are scheduled for fiscal year 2007.
- Upon submission of complete BLAs or supplemental applications.

Action VI.A.1.b: Implement early interactions and communications with sponsors through face-to-face, pre-submission meetings and conferences to provide guidance to encourage novel manufacturing and delivery technologies for the development of pandemic influenza vaccines.

Deliverables:

- A draft guidance document on the requirements of characterizing cell substrates used to manufacture viral vaccines, including cell-based influenza vaccines.
- Expedited scheduling of meetings with sponsors to ensure timely and relevant regulatory guidance.

Timeframe:

- We issued a draft guidance in September 2006. We will complete a review of the comments we receive on the draft in fiscal year 2007 and develop a plan in fiscal year 2007 for issuing a final guidance.
- This is an ongoing activity.

Action VI.A.1.c: Provide information regarding the clinical data needed for the regulatory evaluation and acceptance of seasonal and pandemic influenza vaccines for use as investigational new drugs and as licensed products under a BLA, or other regulatory pathways.

Deliverables:

- Work with NIH and manufacturers to make an H5N1 vaccine available to the public.
- A guidance on the clinical data needed to support licensure of pandemic and seasonal influenza vaccines.

Timeframe:

- We will perform an expedited review upon submission of applications or supplements.
- Two draft guidances issued in March 2006, one for seasonal influenza and the other for pandemic influenza. CBER completed the review of comments received on the drafts in fiscal year 2006 and has developed a plan for finalization in fiscal year 2007.

Action VI.A.1.d: Develop and deliver reference strains and reagents for seasonal influenza to manufacturers.

Deliverables: New influenza virus reassortants²⁵ for use in manufacturing.

Timeframe: This occurs on an annual basis.

Action VI.A.1.e: Develop antisera²⁶ for potency testing.

Deliverables: Strain-specific antiserum and antigen reagents for use in determining vaccine potency and performance of lot-release testing on influenza vaccines prior to their distribution.

Timeframe: This occurs on an annual basis.

Action VI.A.1.f: Standardization of influenza vaccine related tests used for clinical development, vaccine production, and lot release to reduce variability of these tests and to ensure consistent results or outcomes.

Deliverables: Standardized tests.

Timeframe: Research is already underway; progress will depend on research results.

Objective VI.A.2: Conduct post-market surveillance and oversight activities relating to vaccines.

Action VI.A.2.a: Facilitate efforts to increase capabilities for monitoring adverse events in the Vaccine Adverse Events Reporting System (VAERS) and healthcare databases.

Deliverables:

- Work with CDC, manufacturers, and other Federal departments and agencies to detect and monitor adverse events associated with pandemic influenza vaccines.
- A pilot project to expand the Vaccine Safety Datalink database for pandemic influenza vaccine safety surveillance.

Timeframe:

- Implementation of monthly internal reporting of safety surveillance summaries for the seasonal flu vaccine began with first distribution in late summer-early fall 2006.
- We initiated the pilot project in October 2006, and accumulation of data is ongoing.

Action VI.A.2.b: Ensure ongoing optimization of compliance at existing licensed influenza vaccine manufacturing facilities to ensure preparedness for rapid pandemic influenza vaccine production.

Deliverables: Annual (rather than biennial) CGMP inspections of all licensed influenza vaccine manufacturing facilities.

Timeframe: Annual inspections were implemented in fiscal year 2005 and are continuing.

Objective VI.A.3: Assist and coordinate with Federal entities, such as the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), CDC, NIH, and the United States Department of Agriculture (USDA) to encompass various aspects of pandemic influenza planning related to vaccines.

Action VI.A.3.a: Work with HHS to develop a plan for expediting manufacturing expansion and capacity and work with other HHS component agencies, as needed, on issues involving the SNS.

Deliverables:

- A plan for expediting manufacturing expansion and capacity.
- Publication of the interim final rule titled, "Exceptions or Alternatives to Labeling Requirements for Products Held by the Strategic National Stockpile."²⁷

Timeframe:

- A draft plan – "Expansion of Egg-Based Influenza Vaccine Manufacturing Facilities: Compressed Facility Establishment Pathway" – was completed in October 2005. This plan has been used to inform HHS as it considers contracts for egg-based facility expansion.
- FDA clearance of the SNS drug labeling interim final rule occurred in November 2006. The rule is proceeding to HHS and OMB clearance.

Action VI.A.3.b: Explore scientific, legal, and policy issues related to the use of veterinary vaccine facilities to increase human vaccine manufacturing capacity during an emergency.

Deliverables: Engage in discussions with USDA and other regulators regarding the feasibility of the use of veterinary vaccine

facilities for human products.

Timeframe:

- Discussions with USDA occurred in January, March, and April 2006.
- At a WHO-sponsored meeting on April 27, 2006, USDA and FDA, as well as other foreign regulatory agencies and manufacturers, presented information on the use of veterinary facilities for manufacturing human influenza vaccines. Additional WHO-sponsored meetings have discussed a summary of issues pertaining to the use of veterinary facilities.

Objective VI.A.4: Work with industry, foreign public health authorities, and other stakeholders to assess preparedness and to develop strategies for harmonizing, where feasible, regulatory expectations for pandemic influenza vaccines to help increase the speed and efficiency of their development and production.

Action VI.A.4.a: Convene national regulatory authorities from around the world, under the aegis of the WHO, to work towards regulatory preparedness/convergence for pandemic influenza vaccines to maximize response preparedness in the event of an influenza pandemic.

Deliverables:

- FDA, as part of international working groups, will develop strategies and outline a framework of globally consistent regulatory approaches based on the available science.
- Consensus documents representing such an approach.

Timeframe:

- Working group meetings are an ongoing activity.
- A WHO-affiliated meeting hosted by FDA, in Bethesda, Maryland, in June 2006, reviewed draft consensus documents and proposed a plan for the documents' availability in 2007.

Objective VI.A.5: Educate and exchange information with industry, foreign public health authorities, and other stakeholders on regulatory considerations.

Action VI.A.5.a: Establish regular communications with foreign regulatory counterparts under our information sharing agreements.

Deliverables: Exchanges of information and collaboration on technologies and overcoming challenges.

Timeframe: Communications began in February 2006, and subsequent communications occurred in May, July, and November 2006, and March 2007, with additional communications scheduled in 2007.

Action VI.A.5.b: Conduct outreach regarding CGMPs and quality systems to encourage consistent and uninterrupted production of quality vaccines.

Deliverables:

- Presentations and interactions with industry and foreign counterparts on CGMP challenges.

- Conduct a training workshop on CGMPs for foreign regulatory authorities to assist them in their efforts to ensure that CGMPs are applied to the manufacture of vaccines.

Timeframe:

- This is an ongoing activity, with the next meeting scheduled for March 2007, in Barcelona, Spain, and an additional meeting scheduled for August 2007, in Cambridge, Maryland.
- Training workshops will be held in the United States in May 2007.

Action VI.A.5.c: Exchange information with and educate vaccine manufacturers on regulatory considerations.

Deliverables: Organization of and participation in regular "Vaccine Roundtable" meetings.

Timeframe: Meetings are scheduled at regular intervals. The most recent meeting focused on selected topics, ranging from pre-approval through post-approval activities, and occurred in Fall 2006.

Objective VI.A.6: Work with the Office of the Secretary within HHS, CDC, the American Association of Blood Banks (AABB), and other organizations to develop responses to emerging potential threats to the safety and availability of blood, cell, and tissue products needed to support public health and medical care.

Action VI.A.6.a: Enhance existing regular communications and collaborative strategic activities focusing on pandemic influenza preparedness and responses within CBER and within HHS, CDC, and with industry organizations to ensure coordinated responses to emerging potential threats to blood, cell, and tissue product safety and/or availability.

Deliverables: Work with tissue and blood professional organizations and other stakeholders, including the AABB Interorganizational Task Force on Pandemic Influenza and the Blood Supply, to assist their efforts to develop pandemic influenza planning strategies.

Timeframe: CBER actively serves as liaison participants in meetings with key stakeholders. Meetings have occurred in fiscal year 2006 and will continue in fiscal year 2007 to address the safety and availability of blood and tissue products to support public health and medical care.

B. Anti-Viral Drug Development, Production, and Regulatory Review

Unlike vaccines (which are intended to trigger an immune response in the body that will confer some protection against a virus), anti-viral drug products target the virus itself. For example, an anti-viral drug might be designed to interfere with a virus's ability to attach itself to human cells, thereby preventing the virus from infecting the human cells. As another example, an anti-viral drug might be designed to interfere with the virus's ability to replicate itself, either by preventing the virus from releasing or replicating its genetic material or by preventing the virus from releasing viral particles that would then go on to infect other human cells.

Like vaccine development, anti-viral drug development presents its own challenges. In general, understanding how a virus works and/or knowing its composition is very important for anti-viral drug development. For example, assume that a virus has a specific protein sequence on its surface, and the anti-viral drug is designed to bind to that protein sequence to prevent the virus from working properly. It would be important to avoid targeting a protein sequence that also happens to appear in human cells, because then the anti-viral drug could target human cells as well as the virus.

Some drug products might be proposed to act against influenza viruses indirectly, such as influencing host defenses against

infection. Such drug products would go through a development and review process similar to that for drugs with direct anti-viral activity, and the review process would take into account the drug's specific characteristics and mechanism of action.

Although detailed information on a potential pandemic influenza virus is lacking (because an influenza pandemic does not yet exist), we have considerable experience in reviewing and approving anti-viral drug products for numerous viral diseases, including drugs for influenza. Information from the study of an anti-viral drug in circulating influenza is likely to be relevant to potential pandemic influenza strains because the targets of most influenza anti-viral drug products are shared across many viral strains and subtypes. For example, even though it may not be possible to predict how the drug will affect new viral strains, the drug's clinical effects and anti-viral resistance profiles in seasonal influenza outbreaks contribute to the evaluation of the drug's likely utility in future circumstances. Drug development experience with influenza anti-viral drug products in the interpandemic period is, therefore, important to assessing drugs that may be suitable for stockpiling. Agencies and sponsors may also be able to apply and build upon such experience to assess new information that may become available in an influenza pandemic situation as well as for ongoing assessments when the pandemic influenza subtype evolves into circulating seasonal influenza strains after an influenza pandemic.

Anti-viral drugs would be an important part of an influenza pandemic response along with other FDA-regulated products, such as vaccines (which would immunize individuals against a pandemic influenza virus or elicit cross-reactive antibodies) and medical devices, particularly diagnostic devices (which would help confirm whether an individual had contracted the virus and help public health authorities decide how to treat individuals and to prevent further transmission).

Objective VI.B.1: Facilitate anti-viral drug development and regulatory review.

Action VI.B.1.a: Evaluate and analyze initial pre-clinical data on drug safety, efficacy, and viral resistance from pre-IND, IND, and pre-EUA proposals and submissions. Refer potential sponsors in very early development to the National Institute for Allergy and Infectious Diseases's (NIAID) drug screening program. Facilitate communications with sponsors using written responses, teleconferences, or face-to-face meetings, as appropriate to specific situations.

Deliverables:

- Reviews of pre-IND materials, INDs, and pre-EUA submissions.
- Refer potential sponsors to the Web site for the NIAID drug screening program (www.niaid.nih.gov/dmid/viral).
- Advice and comments to sponsors via fax, letter, teleconference, or meeting, as appropriate, based on our review of the submitted material.

Timeframe:

- Our goal is to complete reviews in reduced timeframes.
- We will refer potential sponsors to the Web site in response to inquiries.
- Our goal is to provide advice and comments to sponsors in a timely manner as appropriate to the submission's contents.

Action VI.B.1.b: Provide advice to industry and other Federal departments and agencies on clinical trial designs to evaluate the safety and efficacy of new anti-viral drug products or new formulations or dosing regimens of existing anti-viral drug products.

Deliverables:

- We will provide regulatory advice to industry and other Federal departments and agencies regarding the design of clinical trials

of existing and new anti-viral drug products against influenza.

- Review of clinical trial protocols to test anti-viral drug products for safety and efficacy during the interpandemic period.
- Advice and comment on protocol design for multi-center and multi-national, randomized clinical trials.

Timeframe: We have already reviewed several protocols in fiscal year 2006 and, as appropriate, have provided advice on development questions. Future timelines in fiscal year 2007 and beyond for the deliverables mentioned immediately above will be as appropriate to the submissions received. Our goal is to provide prompt responses.

Action VI.B.1.c: Review pre-EUA, IND, NDA, or BLA submissions and public or non-public information in support of potential uses of unapproved anti-viral drug products under an IND or EUA.

Deliverables:

- A Standard Operating Procedure (SOP) for issuing an EUA.
- Updates to our existing application tracking systems to accept pre-EUA submissions.
- Reviews of information from pre-EUA submissions, INDs, NDAs, and BLAs, and labeling, as appropriate.

Timeframe:

- We will prepare a SOP in fiscal year 2007.
- We will update the application tracking system by the first quarter of fiscal year 2008.
- We will expedite reviews as appropriate to the information submitted and the pandemic influenza phase.

Action VI.B.1.d: Provide information on our Web site (<http://www.fda.gov/cder/ode4/preind/default.htm>) to encourage early pre-IND interactions.

Deliverables: An updated Web site.

Timeframe: We have already posted updated contact information and links to drug label information. We will post additional updates as new information becomes available.

Objective VI.B.2: Expedite review of NDAs, BLAs, abbreviated new drug applications (ANDAs), and supplements for anti-viral drug products that may be relevant to preparedness for an influenza pandemic.

Action VI.B.2.a: Prioritize pandemic influenza-related submissions in the Office of Generic Drugs (OGD), consistent with OGD review procedures.

Deliverables: A template memorandum for expected ANDA submissions in anticipation of their receipt. (The memorandum would seek permission from the Director of CDER to raise the review priority in OGD.)

Timeframe: CDER prepared and cleared a template memorandum in fiscal year 2006.

Action VI.B.2.b: Employ expedited review mechanisms for NDAs, BLAs, ANDAs, and supplements, as appropriate.

Deliverables: Rapid completion of reviews and labeling.

Timeframe: We will complete reviews consistent with priority review or other available expedited review mechanisms.

Objective VI.B.3: Identify new targets for influenza viruses that may lead to identification of new classes of anti-viral drug products, and evaluate alternative drug development pathways, including the use of biomarkers and animal models that may expedite the availability of novel and promising anti-influenza therapies.

Action VI.B.3.a: Actively consider input from the scientific community by working with NIH/NIAID and participating in an expert panel on influenza to better understand the current challenges and opportunities in anti-viral drug development. The desired outcomes are:

- To help FDA in considering:
- Whether there are animal models of influenza that will adequately predict human disease and responses;
- Animal models for studying novel viral strains to support and supplement clinical trial data in naturally occurring disease;
- The relative contributions of studies in which volunteers have been exposed to weakened laboratory strains of a virus to test the effects of anti-viral drugs (challenge studies); and
- The appropriate design of clinical trials to maximize the efficient acquisition of data.
- To support IND and EUA uses in emergency situations, as appropriate.

Deliverables: Participation in an NIH/NIAID expert panel.

Timeframe: An expert meeting, with invited FDA participation, was convened by NIH/NIAID in November 2006.

Action VI.B.3.b: Clarify the recommendations for pre-EUA submissions for pandemic influenza anti-viral drug products.

Deliverables: A concept paper that provides recommendations on how an anti-viral drug product can be eligible for an EUA and advice, on a case-by-case basis, in response to product-specific inquiries.

Timeframe: Active planning and initial drafting of the concept paper by the end of the second quarter of fiscal year 2007, with revisions as appropriate depending on the development of additional relevant information. We will provide advice in response to product-specific inquiries, as appropriate to the inquiries received.

Action VI.B.3.c: Use scientific information from expert meetings, literature, etc., to identify and prioritize anti-influenza drug development issues.

Deliverables: A list of issues with discussion points.

Timeframe: We included information from literature articles in the discussion of NIH/NIAID panel meeting plans during fiscal years 2006 and 2007. Monitoring of issues from the literature is an ongoing activity.

Objective VI.B.4: Facilitate product manufacturing and capability to address surge capacity.

Action VI.B.4.a: Facilitate the expansion of domestic manufacturing capacity to produce anti-viral drugs against influenza.

Deliverables:

- Work with current manufacturers of anti-viral drug products to expand domestic production.
- Identification of possible mechanisms, if needed, to permit other manufacturers to produce proprietary anti-viral drug products, including discussion of sublicense proposals from existing manufacturers.
- Identification of alternate manufacturers capable of performing rate-limiting steps in manufacture.
- Expedited inspections of new manufacturing sites.
- Expedited review of information related to new manufacturing sites and manufacturing processes and controls.

Timeframe: This is an ongoing activity with deliverables related to manufacturer-initiated submissions. Our goal is to complete reviews in reduced timeframes. Preliminary discussions of sublicense proposals have taken place, and we will update them as appropriate to information becoming available. We have reviewed several manufacturing supplements already.

Action VI.B.4.b: Monitor drug supply issues and maintain a database of supply status and production capacity to enhance anticipation and assessment of shortages.

Deliverables: Updates on supply and shortage issues and our Critical Products Program database.

Timeframe: We have updated the Critical Products Program database in fiscal year 2006 and will update it, as appropriate, thereafter. We will provide updates on shortage issues as needed in response to reports of expected or actual shortage situations.

Objective VI.B.5: Active monitoring and passive surveillance of adverse events reported with anti-viral drug products used for pandemic influenza.

Action VI.B.5.a: Work with HHS agencies to use existing surveillance systems, such as MedWatch, and develop post-emergency surveillance plans.

Deliverables:

- A post-emergency surveillance plan.
- Review of adverse event reports submitted to MedWatch associated with anti-viral drug products used for pandemic influenza.
- Active monitoring for adverse events among patients presented for care in a network of emergency departments. This monitoring will occur through the existing National Electronic Injury Surveillance System Cooperative Adverse Drug Event Project maintained by CDC and FDA.

Timeframe:

- Active discussions during fiscal year 2007 for the surveillance plan, with the plan's final form subject to revision as more information becomes available.
- Final review of influenza anti-viral drug adverse events from the 2005-2006 influenza season by fourth quarter of fiscal year 2007 and as appropriate to the level of the influenza season and reporting activity thereafter.
- Monitoring adverse events is an ongoing activity.

Objective VI.B.6: Facilitate the deployment of stockpiled drugs in the event of an influenza pandemic.

Action VI.B.6.a: Work with the CDC's Coordinating Office for Terrorism Preparedness & Emergency Response, Division of the Strategic National Stockpile (COTPER/DSNS) and industry, repackagers, and relabelers to facilitate advance development of

packaging, labeling, and specialized instructions if there are requests to modify any of these for the purpose of addressing stockpile-specific storage or distribution issues for products which are in the stockpile or may be added to the stockpile. Respond to the CDC's COTPER/DSNS on the regulatory status of proposed novel packaging and labeling of anti-viral drug products. For example, new labeling may be necessary when investigational new drug products in the SNS are approved or licensed, or new, yet unapproved, packaging (such as unit of use or unit dose packaging) may be necessary in order to distribute a product effectively during a public health emergency.

Deliverables:

- We have provided and will continue to provide a response or a plan of action to the CDC's COTPER/DSNS on inquiries regarding repackaging and relabeling.
- Priority review and action, as appropriate, on NDA supplements for packaging changes.

Timeframe:

- During an influenza pandemic alert period, we will expedite the request for technical advice and provide a response no later than 60 days of receipt of an inquiry and as appropriate to the urgency of the matter.
- During an influenza pandemic alert period, we will review NDA supplements for packaging changes on a priority basis as appropriate.

Action VI.B.6.b: Participate in an interagency working group to develop specific recommendations for anti-viral drug products to include in Federal and non-Federal stockpiles.

Deliverables: Technical advice on scientific and regulatory issues, as appropriate, during discussion and drafting of the recommendations.

Timeframe: We will provide advice within 60 days of receipt of a request.

Action VI.B.6.c: Work with the CDC's COTPER/DSNS to determine the eligibility of future stockpiled products for the SLEP.

Deliverables:

- We will address requests from the CDC's COTPER/DSNS for the eligibility of future stockpiled products for participation in the SLEP.
- Work with SNS and SNS contractors to develop new expiry labeling to facilitate SLEP compliance.

Timeframe:

- We will address requests from the CDC's COTPER/DSNS for the eligibility of future stockpiled products for SLEP within 60 days.
- We will respond to SNS and SNS contractors' requests to develop new expiry labeling within 60 days of a request.

Action VI.B.6.d: Consider expanding the existing SLEP beyond the Federal government.

Deliverables:

- A determination regarding the extension of SLEP beyond the Federal government.

Timeframe:

- The determination whether to extend SLEP was made first quarter of fiscal year 2007.

Action VI.B.6.e: Develop an after-action report addressing deployment of FDA-regulated products from the SNS.

Deliverables: A completed report pertaining to FDA-regulated products after the first wave of products has been deployed from the SNS.

Timeframe: Within 90 days after an event of such significance that it requires deployment of FDA-regulated products from the SNS.

Action VI.B.6.f: Coordinate with other Federal departments and agencies and State, local, and tribal public health departments that are developing plans to store anti-viral drug products at the SNS or at other designated sites and will be distributing anti-viral products through private distributors and/or other carriers to designated sites. FDA's input would be to help ensure proper conditions that comply with the product's labeled storage conditions.

Deliverables: Consultations with pharmaceutical manufacturers and distributors and with State, local, and tribal public health departments on possible storage facilities and storage requirements.

Timeframe: Fiscal year 2007.

C. Device Development, Production, and Regulatory Review

Like vaccines and anti-viral drug products, devices would play an important role in an influenza pandemic. Rapid diagnostic devices, for example, are critical components of an effective pandemic influenza preparedness and response program. Diagnostic devices, by helping determine whether a person was infected with a pandemic influenza virus (as opposed to a seasonal influenza virus), would serve as a disease monitoring tool and help healthcare professionals determine the best treatment for that individual. Diagnostic devices could also help determine which infection control measures to pursue (such as immunizing individuals in a specific area after diagnostic devices had confirmed that an individual in that area had contracted a pandemic influenza virus) and other public health responses to reduce the spread of disease. PPE devices, such as masks and gloves, could help prevent infection among healthcare professionals and, as a result, prevent the loss of valuable medical expertise and resources at a time when the demands on healthcare resources would be great. Other devices, such as ventilators and endotracheal tubes, may help relieve symptoms in persons affected by pandemic influenza or help their recovery.

Devices can present unique challenges or considerations, too. For example, can the device be used more than once and still remain safe and effective? If the device is intended to deliver a drug, will it be able to deliver an anti-influenza drug in a manner that does not affect the drug's safety or effectiveness?

We have considerable experience with device development, production, and regulatory review. For example, on February 3, 2006, we cleared a new laboratory test to diagnose H5 influenza strains in patients suspected of being infected with the virus. The test, known as the Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set, will give preliminary results on

suspected samples within hours; this represents a significant improvement over earlier testing technologies that required two to three days before producing results.

The Medical Device User Fee Modernization Act (MDUFMA) has better positioned FDA to review new devices more effectively and efficiently. MDUFMA supports close collaboration with stakeholders and increased communications with applicants. These efforts help applicants improve the quality of their submissions to FDA and help us provide more rapid, better-focused reviews. Our ultimate objective is to make important new safe and effective medical devices available to patients and health care providers more quickly while continuing to ensure device quality, safety, and effectiveness once a product is on the market.

Objective VI.C.1: Facilitate development and regulatory review of influenza-related devices, including diagnostics and PPE devices.

Action VI.C.1.a: Implement early interactions and communications with sponsors through face-to-face, pre-submission meetings and conference calls.

Deliverables:

- Expedited scheduling of meetings with sponsors.
- Greater meeting opportunities for sponsors.

Timeframe: This is an ongoing activity.

Action VI.C.1.b: Timely review and approval or clearance of devices.

Deliverables: Expedite review of devices that may be needed for an influenza pandemic, as appropriate.

Timeframe: This is an ongoing activity.

Action VI.C.1.c: Work with manufacturers to help ensure compliance with quality systems regulations (QSRs).

Deliverables:

- Identification of device manufacturers with QSR issues that would or could affect safety and effectiveness. We will work with such manufacturers to address quality issues.
- For those manufacturers with identified QSR issues, coordination and expedited scheduling and performance of inspections for PPE, influenza-related diagnostics, and other support devices such as ventilators, resuscitator bags, and endotracheal tubes.

Timeframe: This is an ongoing activity.

Objective VI.C.2: Anticipate shortages and support efforts to prevent shortages of key devices.

Action VI.C.2.a: Work with manufacturers to support efforts to ensure an adequate supply of diagnostics, PPE, and other devices that are expected to be in high demand during influenza outbreaks and for which short supplies are predicted.

Deliverables:

- Continuous liaisons with manufacturers and coordination with other HHS agencies or working groups to address medical products supply and availability.
- Updates to the list of the devices commonly used to manage influenza patients, including devices used for infection control. Identification of the devices that may be in short supply if demand increases.
- Updated contact information on manufacturers and the estimated number of select products available for immediate distribution, as well as the time that would be necessary to increase production to meet public health needs. We will verify the information every six months to ensure its accuracy.

Timeframe:

- Continuous liaisons with manufacturers and coordination with other HHS agencies or working groups is an ongoing activity.
- We prepared a list of devices in September 2006. Updating the list is an ongoing activity.
- We prepared contact information on manufacturers and the estimated number of select products in September 2006. Updating the contact information is an ongoing activity.

Objective VI.C.3: Ensure continued safety and effectiveness of influenza-related devices during the post-market phase of the product life-cycle.

Action VI.C.3.a: Continue post-market monitoring and data analysis of adverse event reports on influenza-related devices to ensure the continued safety and effectiveness of marketed devices.

Deliverables:

- Prompt action on evidence of potential harm or increased risk to users of these devices.
- Exchange of relevant information, as needed, with foreign regulatory authorities.
- Continuous education of professionals and consumers on adverse event reporting mechanisms.

Timeframe: This is an ongoing activity.

Action VI.C.3.b: Require, as appropriate, post-market studies or information gathering on influenza-related devices. This can be accomplished in three different ways depending on the type of product involved and the applicable regulatory requirements. It may be required: (1) under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360l) and 21 CFR part 822, provided that the statutory and regulatory criteria are satisfied; (2) as a special control; or (3) as a condition of approval for class III devices.²⁸

Deliverables: Work with manufacturers in the planning of post-market studies, as appropriate, and provide recommendations on the types of useful data to be collected in these studies.

Timeframe: We will provide recommendations within 60 days after receiving the premarket submission.

Objective VI.C.4: Educate device users on how to use influenza-related devices in a safe and effective manner.

Action VI.C.4.a: Develop educational materials on the uses of these devices, including appropriate warnings, precautions, and limitations.

Deliverables:

- Consultation with other agencies, such as CDC (including the National Institute for Occupational Safety and Health), the Occupational Safety and Health Administration (OSHA), and the Environmental Protection Agency (EPA), which may also provide advice regarding the selection and use of these devices, to ensure accurate and consistent messages.
- The posting of new informational material and the updating of existing material on our Web site.

Timeframe:

- Consultation with other Federal departments and agencies is an ongoing activity.
- Posting of new informational material occurred in June 2006 and September 2006. We will post updates as new information becomes available.

Objective VI.C.5: Enhance communication with stakeholders

Action VI.5.a: Communicate FDA influenza-related device activities and information to industry, consumers, State, local, and tribal governments and other stakeholders. Collaborate with other Federal and international health agencies on public messages related to the use of influenza-related devices to ensure consistency and accuracy.

Deliverables: Influenza information on our Web site that is up-to-date and consistent with information disseminated by other Federal and international agencies.

Timeframe: This is an ongoing activity.

D. Food and Feed Safety²⁹

In general, national and international public health authorities and organizations believe that human consumption of properly cooked or prepared food poses no risk of acquiring AI. However, birds are capable of transmitting AI to other birds, and there is some evidence suggesting that felids³⁰ can become infected after eating raw, infected birds.

As an agency with significant responsibilities to protect human food and animal feed, we have a role in determining whether the AI virus presents a risk to human food or animal feed (due to the use of avian-derived ingredients in the food or feed) and in identifying methods to inactivate the AI virus in food or feed. Our experience with other foodborne pathogens (such as *Salmonella enterica*, serovar Enteritidis) and novel diseases (such as bovine spongiform encephalopathy (or "mad cow" disease)) will be helpful in dealing with the AI virus and a possible human pandemic influenza virus.

Objective VI.D.1: Assess the likelihood of food and feed contamination with highly pathogenic avian and human pandemic influenza virus.

Action VI.D.1.a: Monitor global avian influenza activity in wild and domestic avian species and pandemic influenza activity in humans to identify the potential for food and/or feed contamination.

Deliverables:

- Stronger collaboration with and communication on influenza surveillance with CDC and USDA.
- Sharing of information with other Federal, State, local, and tribal government departments and agencies and international public

health and animal health organizations.

Timeframe: This is an ongoing activity.

Action VI.D.1.b: Identify FDA-regulated foods (including dietary supplements) and animal feeds that are at elevated risk of contamination with infectious AI or pandemic influenza virus.

Deliverables:

- A list of FDA-regulated foods and feed ingredients that contain avian-derived materials.
- Identification of foods (in addition to whole shell eggs) that contain domestic or imported avian-derived ingredients.
- A determination of the risk of contamination of food derived from marine and freshwater fish and shellfish from harvest waters that are potentially contaminated by infected waterfowl and domestic poultry.
- An estimate of the likely level and frequency of contamination of ready-to-eat foods by infectious respiratory droplets from human cases of pandemic influenza.

Timeframe: Began in fiscal year 2006.

Action VI.D.1.c: Investigate the effectiveness of food and feed processing and preparation practices for inactivating influenza viruses by:

- Determining typical food processing and preparation practices for FDA-regulated foods that contain eggs and avian tissues;
- Conducting a literature search on the survivability of influenza viruses in various conditions and in various food and feed matrices;
- Working with USDA's Agricultural Research Service (ARS) to determine the upper limits of virus titers in egg contents for various HPAI strains and time/temperature requirements for the inactivation of different HPAI strains in eggs and meat from game birds;
- Communicating with the egg industry to determine temperatures achieved during different cooking methods for eggs;
- Conducting in-house research on cooking and other processing methods to determine their effectiveness in inactivating influenza virus strains of interest in food; and
- Collecting information on current procedures and practices used for the treatment of poultry litter intended for use in animal feed.

Deliverables: Up-to-date information on conditions necessary in food and feed processing for the inactivation of influenza viruses.

Timeframe: Initial literature searches completed in fiscal year 2006, with additional data expected during fiscal years 2007 and 2008.

Action VI.D.1.d: Develop analytical methods, reagents, and testing capability for identifying influenza virus in foods, as appropriate to protect the human food supply.

Deliverables: Publication of validated methods for detecting influenza virus in FDA-regulated foods.

Timeframe: Completion will occur in fiscal years 2008 and 2009.

Action VI.D.1.e: In coordination with ORA, establish inspection plans for food and feed and, as appropriate, sampling plans for foods based on the potential for contamination by AI viruses and availability of laboratory methods. Work with other Federal and State departments and agencies to enhance and increase the number of inspections of domestic products at elevated risk of contamination with AI viruses and imports from affected countries.

Deliverables:

- Inspection plans for foods and feed.
- Sampling plans for analysis of potentially contaminated foods and, if identified, foods associated epidemiologically with human illness.

Timeframe: Fiscal year 2008.

Objective VI.D.2: Enhance communication with stakeholders.

Action VI.D.2.a: Communicate our influenza-related food and feed safety activities and information to industry, consumers, State, local, and tribal governments, and other stakeholders. Collaborate with other Federal and international human/animal health departments and agencies on public messages related to AI and food and feed safety to ensure consistency and accuracy.

Deliverables: Influenza information on our Web site that is up-to-date and consistent with information disseminated by other Federal and international departments and agencies.

Timeframe: This is an ongoing activity. We will update the Web site on an as needed basis.

Action VI.D.2.b: Exchange with other Federal departments and agencies emerging data on the geographic distribution of AI strains of interest and of pandemic human strains, the tissue distribution of the AI virus, and the effects of factors important in food processing and preparation (e.g., temperature, pH, salt concentration) on inactivation of these viral strains.

Deliverables: Establishment of an information sharing forum with interagency membership, as appropriate.

Timeframe: We established the forum in fiscal year 2006

Action VI.D.2.c: Enhance biosecurity measures for the food, feed, and rendering industries to meet any additional risks posed by AI or an influenza pandemic. Work with industry, Federal, State, local, and tribal departments and agencies, and others on biosecurity strategies. Identify and review existing biosecurity documents. Provide technical assistance to industry as it implements biosecurity measures. Work with USDA, EPA, and State, local, and tribal governments on disposal options for birds and potentially contaminated materials from infected flocks.

Deliverables:

- "Best practices" guidance documents for the food, feed, and rendering industries, as needed.
- A final rule on shell egg *Salmonella* Enteritidis prevention.

Timeframe: Fiscal year 2007.

Objective VI.D.3: Preserve the effectiveness and supply of drugs approved for the prophylaxis and treatment of influenza

in humans.

Action VI.D.3.a: Prohibit the extra-label use of human influenza anti-viral drug products in chickens, turkeys, and ducks.

Deliverables: An order prohibiting the extra-label use of influenza anti-viral drug products of the adamantane and neuraminidase inhibitor drug classes in chickens, turkeys, and ducks.

Timeframe: We issued a final rule on March 22, 2006 in the *Federal Register* (71 FR 14374). The final rule became effective on June 20, 2006. We may expand the list of animal species affected as new data become available.

Action VI.D.3.b: Educate producers, veterinarians, the feed industry, and others about the public health threat posed by the use of human influenza anti-viral drug products in animals, and provide information about relevant prohibitions.

Deliverables: Collaboration with veterinary and producer organizations, international organizations, foreign governments, and others to disseminate information. This collaboration may take several forms, such as meetings, presentations to professional societies and to academia, and notifications to OIE member countries.

Timeframe: This is an ongoing activity.

Action VI.D.3.c: Provide testing capability for anti-influenza drug residues in avian-origin foods, as appropriate to protect the public health.

Deliverables:

- Validated analytical methods to detect and identify residues of influenza anti-viral drug products in the adamantane and neuraminidase drug classes in poultry.
- Collaboration with the Central Science Laboratory³⁰ of the United Kingdom's (U.K.'s) Department for Environment, Food, and Rural Affairs (Defra) to develop and validate methods.
- Assistance in technology transfer to other public health laboratories.

Timeframe: Fiscal year 2007-2008.

Action VI.D.3.d: Enforce the final rule prohibiting the extra-label use of influenza anti-viral drug products in chickens, turkeys, and ducks. Assess the need for surveillance for human anti-influenza drug use in animals.

Deliverables: Surveillance plan and regulatory actions, as indicated.

Timeframe: This will be an ongoing activity.

E. Emergency Preparedness, Response, and Communication

While much of our plan focuses on vaccines, anti-viral drug products, and devices that might be used to prevent or treat pandemic influenza and on protecting food and feed, we are conscious of the potential impact on society as a whole. For example, if an influenza pandemic causes a large number of illnesses and deaths, there may be an impact on public health services (as more individuals seek or need health care), transportation and business operations (as individuals may choose to stay home rather than travel or go to work), and other societal functions.

Consequently, consistent with the National Strategy for Pandemic Influenza and the HHS Pandemic Influenza Plan, we are prepared to continue essential FDA functions if an influenza pandemic occurs. Our preparations build upon our experience with continuity of operations plans designed to ensure the continuance of essential government functions across a wide range of potential emergencies. The Continuity of Operations Plan (COOP) for the Office of the Commissioner (dated December 12, 2003) identifies and provides specifics on essential functions, leadership succession, delegation of authority, performance of work at alternate work sites, and other matters related to how we will operate in the face of any emergency, including an influenza pandemic.

These preparations are especially important in our efforts to ensure that our workforce is ready to deliver critical program support services under extremely adverse conditions. Detailed planning is underway to ensure that key management functions continue through an influenza pandemic. These management functions include: ensuring information technology (IT) infrastructure support (including work-at-home scenarios); providing critical financial services (such as employee payroll, vendor payments, and reprogramming of financial resources to pandemic influenza response), as needed; preparing emergency spending appropriations requests; ensuring that FDA facilities are safe and habitable for our employees; and acquiring critical pandemic influenza response supplies and services through our contracting operations. In addition, we outlined our roles and responsibilities as part of HHS' coordinated interagency operational plan, Part II of the HHS Pandemic Influenza Implementation Plan.

We also recognize that communication – with individuals, healthcare providers, employees, and the media – will be important to convey clear, accurate, and science-based information that enables individuals to learn about the disease and available treatments.³² We will deploy our crisis communication plan if necessitated by instances such as a food-borne illness or promotion of fraudulent therapies or practices. Communication will also enable individuals to learn about steps they may take to protect themselves and can generate and increase public trust and confidence. We are fortunate to have an extensive array of communications tools at our disposal, including:

- Our Web site (www.fda.gov) where we can post the latest documents and FDA information and provide electronic access to various newsletters and webcasts,
- Satellite broadcasts and video productions which our Office of Public Affairs is capable of producing,
- *FDA Consumer*, which is FDA's official magazine and reports on current agency activities and public health issues, and
- Press releases, "Talk Papers,"³³ information sheets, and other documents.

Objective VI.E.1: Ensure relevant agency operational and response plans are adequate for use if an influenza pandemic occurs and ensure these plans address the unique workplace situations an influenza pandemic would present compared to other types of emergencies.

Action VI.E.1.a: Integrate components from business recovery, continuity of government, continuity of operations, and disaster recovery plans into pandemic influenza plans as appropriate.

Deliverables:

- FDA Pandemic Influenza Emergency Response Plan (draft).
- Submission of an FDA Operational Plan to the Department of Health and Human Services as an annex to the HHS Pandemic Influenza Implementation Plan – Part II.
- Exercise(s) to test the FDA Pandemic Influenza Emergency Response Plan and agency or center continuity of business operations plans.

Timeframe:

- First quarter of fiscal year 2008 for the FDA Pandemic Influenza Emergency Response Plan draft.
- The FDA Operational Plan was submitted to the Department of Health and Human Services in December 2006, and was incorporated into Part II of the HHS Pandemic Influenza Implementation Plan.
- Second quarter of fiscal year 2008 for the exercise(s).

Objective VI.E.2: Inform our employees about our plans for maintaining business operations in the event of an influenza pandemic and provide updated information to our employees throughout the pandemic. Reassure our employees that we are attentive to their health, safety, and economic vitality.

Action VI.E.2.a: Communicate with our employees about individual responsibility, mission travel, vaccine administration, anti-viral drug products, and work at home/shelter at home. Involve the National Treasury Employees Union, as appropriate, regarding significant changes in working conditions.

Deliverables: An established protocol for the use of electronic mail (e-mail) to inform employees.

Timeframe: We established a specific Office of Management Pandemic Influenza Preparedness Protocol on March 6, 2007, that provides regular electronic updates via e-mail, BlackBerry, and Internet Outlook Web Access. This protocol includes ongoing support with a recorded status line and call center response via phone or Intranet. Protocol services are supported by our Employee Resources and Information Center.

Objective VI.E.3: Ensure we develop and issue FDA-specific public health messages and reports of our accomplishments in coordination with HHS and align with related HHS public health messages.

Action VI.E.3.a: Coordinate with HHS expedited development and dissemination of public information.

Deliverables: A Strategic Communications Plan.

Timeframe: Fiscal year 2007.

Objective VI.E.4: Assess how we can use our inventories of FDA-regulated establishments that prepare, pack or hold commercially distributed drugs, biological products (including blood), devices, and feed if disruptions occur in the commercial shipment of such products.

Action VI.E.4.a: Create subsets of FDA product line (i.e., drugs, biological products, etc.) inventories. From the inventory subsets, create geo-coded maps (maps in which geographic identifiers have been assigned) for identifying major industry sources that can respond if product shortages occur.

Deliverables: Up-to-date regional establishment lists and software upgrades and geo-coded maps of FDA-regulated establishments.

Timeframe: Geo-coded maps were created for all product subsets and provided to FDA field offices by the first quarter of fiscal year 2007. Updates to the maps will be provided on a monthly basis or sooner if needed. Additional software upgrades were made in the first quarter of fiscal year 2007 which will increase the speed and size of map development.

Action VI.E.4.b: Help OGHHA and ASPR, Office of the Secretary (OS), HHS, to complete protocols of mutual assistance in the event of a cross-border emergency with Canada and Mexico.

Deliverables: OS, under the Health Working Group of the Security and Prosperity Partnership of North America, has the lead for

HHS.

- FDA will provide technical input to OS/HHS, on text for the protocol pertaining to the acceptance, in an emergency, of stockpiled drugs, vaccines, and medical supplies from the Canadian national stockpile.

Timeframe: Provide technical input to OGHA and ASPR, in a timely manner in response to their requests, so as to contribute to the OS/HHS deadline to complete the protocol by June 1, 2007.

F. Enforcement

Federal law requires that many FDA-regulated products, including drugs, biological products, and devices, be shown to be both safe and effective for their intended uses before entering the market. These requirements protect American consumers, yet our experience has shown that unscrupulous individuals or firms may attempt to avoid complying with safety and efficacy requirements by selling fraudulent or counterfeit products, particularly when there is a new disease and there are no approved products to treat the new disease or where an approved product is in great demand or expensive to buy.

Fraudulent and counterfeit products can be unsafe due to the presence of contaminants and dangerous ingredients. They also may be ineffective because:

- In the case of drugs, they lack the drug's active ingredient or sufficient quantities of the drug's active ingredient;
- In the case of vaccines, they lack the vaccine's immunostimulating properties or sufficient quantities of the vaccine's immunostimulating properties; or
- In the case of drugs, biological products, and devices, they have not been shown to work against the disease or pathogen in question.

They can also harm consumers by delaying their access to or use of products that are safe and effective.

With respect to pandemic influenza, since December 2005, we sent Warning Letters to several firms who had made unproven claims that their products would treat or prevent "avian flu" or other forms of influenza.³⁴ In conjunction with U.S. Customs and Border Protection, we have intercepted shipments of a fraudulent "generic" anti-viral drug; the "drug" did not contain an active drug ingredient, but instead contained vitamin C and other ineffective substances.³⁵ Additionally, our Office of Criminal Investigations has worked with Federal and State law enforcement agencies regarding counterfeit, unlicensed, or unauthorized seasonal influenza vaccines.

Objective VI.F.1: Investigate and pursue enforcement action against fraudulent or counterfeit products.

Action VI.F.1.a: Use a risk-based approach to investigate reports of, and pursue enforcement action against, fraudulent or counterfeit products, particularly those that present a high risk to consumers.

Deliverables:

- Development of models to identify and prioritize targets.
- Removal of fraudulent and counterfeit products related to pandemic influenza and AI from the market.
- Evaluation of enforcement activities and accomplishment reports.

Timeframe:

- Target selection and prioritization model in place by the second quarter of fiscal year 2007.
- Enforcement actions are an ongoing activity.
- Evaluation of enforcement activities and accomplishment reports will occur at least quarterly.

Action VI.F.1.b: In collaboration with the Department of Homeland Security (DHS), Department of Justice (DOJ), Department of State (DOS), and Department of Commerce (DOC), investigate and prosecute counterfeit drug cases and enforce Federal laws regarding counterfeit drugs, biological products, vaccines, devices, and other products used in a pandemic influenza situation.

Deliverables: Investigation of reports of counterfeit drugs used for pandemic influenza treatment or for prophylactic purposes and prosecution of cases as evidence warrants.

Timeframe: This is an ongoing activity.

Action VI.F.1.c: In conjunction with DHS, DOJ, DOS, and DOC, institute an expanded plan for investigating and prosecuting cases involving counterfeit seasonal influenza drugs during an influenza pandemic. This includes development of a joint strategic plan for the detection, at the border, of international shipments of counterfeit vaccines and anti-viral drug products.

Deliverables:

- A joint strategic plan for interdicting or preventing international shipments of counterfeit vaccines and anti-viral drug products.
- Prevention or interdiction of international and domestic counterfeit drug shipments.
- Expansion of and updates to a plan of action to handle counterfeit drugs.
- Filing of indictments for cases involving these counterfeit drugs.

Timeframe:

- We will develop a draft plan by the third quarter of fiscal year 2007.
- Prevention or interdiction of counterfeit drug shipments is an ongoing activity.
- We will develop a draft plan of action to handle counterfeit drugs by the second quarter of fiscal year 2007.
- Filing of indictments is an ongoing activity.

Action VI.F.1.d: Increase public awareness of fraudulent or counterfeit products relating to pandemic influenza and AI.

Deliverables:

- Press releases and public advisories.
- Accomplishment reports.

Timeframe:

- We will issue press releases and public advisories as we take enforcement actions.
- We will prepare accomplishment reports at least quarterly.

VII. Tables of FDA Objectives and Actions

**Table 1. Vaccine Development, Production and Regulatory Review Subgroup:
Pandemic Influenza Preparedness Objectives, Actions, Deliverables and Timeframes**

Vaccine and Other Biologics Development, Production and Regulatory Review				
National Strategy Actions³⁶	Objective	Action	Deliverable	Timeframe
6.1.6, 6.1.8, 6.1.10, 6.1.11, 6.1.13, 6.1.16, 6.1.17	Facilitate vaccine development, production, and regulatory review.	Assist efforts to increase manufacturing capacity and product diversity through meetings with vaccine manufacturers. The meetings will address issues such as facility design, non-clinical and clinical studies, and manufacturing.	Meetings with vaccine manufacturers to discuss design plans for vaccine facilities.	Initial meetings with manufacturers to provide guidance on vaccine facility design and commissioning began in 2004. Routine follow-up discussions occurred in fiscal year 2006 and are scheduled for fiscal year 2007.
			Expedited review of BLAs and supplemental applications that could increase both the number of manufacturers and the overall supply of vaccine.	Upon submission of complete BLAs or supplemental applications.
		Implement early interactions and communications with sponsors through face-to-face, pre-submission meetings and conferences to provide guidance to encourage novel manufacturing and delivery technologies for the development of pandemic influenza vaccines.	A draft guidance document on the requirements of characterizing cell substrates used to manufacture viral vaccines, including cell-based influenza vaccines.	We issued a draft guidance in September 2006. We will complete a review of the comments we receive on the draft in fiscal year 2007 and develop a plan in fiscal year 2007 for issuing a final guidance.
			Expedited scheduling of meetings with sponsors to ensure timely and relevant regulatory guidance.	This is an ongoing activity.
			Provide information regarding the clinical data needed for the regulatory evaluation and acceptance of seasonal and pandemic influenza vaccines for use as investigational new drugs and as licensed products under a	Work with NIH and manufacturers to make an H5N1 vaccine available to the public.
			A guidance on the clinical data needed to	Two draft guidances issued in March 2006,

	BLA, or other regulatory pathways.	support the licensure of pandemic and seasonal influenza vaccines.	one for seasonal influenza and the other for pandemic influenza. CBER completed the review of comments received on the drafts in fiscal year 2006 and has developed a plan for finalization in fiscal year 2007.
	Develop and deliver reference strains and reagents for seasonal influenza to manufacturers.	New influenza virus reassortants ³⁷ for use in manufacturing.	This occurs on an annual basis.
	Develop antisera ³⁸ for potency testing.	Strain-specific antiserum and antigen reagents for use in determining vaccine potency and performance of lot-release testing on influenza vaccines prior to their distribution.	This occurs on an annual basis.
	Standardization of influenza vaccine related tests used for clinical development, vaccine production, and lot release to reduce variability of these tests and to ensure consistent results or outcomes.	Standardized tests.	Research is already underway; progress will depend on research results.
Conduct post-market surveillance and oversight activities relating to vaccines.	Facilitate efforts to increase capabilities for monitoring adverse events in the Vaccine Adverse Events Reporting System (VAERS) and healthcare databases.	Work with CDC, manufacturers, and other Federal departments and agencies to detect and monitor adverse events associated with pandemic influenza vaccines.	Implementation of monthly internal reporting of safety surveillance summaries for the seasonal flu vaccine began with first distribution in late summer-early fall 2006.
		A pilot project to expand the Vaccine Safety Datalink database for pandemic influenza vaccine safety surveillance.	We initiated the pilot project in October 2006, and accumulation of data is ongoing.
	Ensure ongoing optimization of compliance at existing licensed influenza vaccine manufacturing facilities to ensure preparedness for rapid pandemic influenza vaccine	Annual (rather than biennial) CGMP inspections of all licensed influenza vaccine manufacturing	Annual inspections were implemented in fiscal year 2005 and are continuing.

	production.	facilities.	
Assist and coordinate with Federal entities, such as the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), CDC, NIH, and the United States Department of Agriculture (USDA) to encompass various aspects of pandemic influenza planning related to vaccines.	Work with HHS to develop a plan for expediting manufacturing expansion and capacity and work with other HHS component agencies, as needed, on issues involving the SNS.	A plan for expediting manufacturing expansion and capacity.	A draft plan – "Expansion of Egg-Based Influenza Vaccine Manufacturing Facilities: Compressed Facility Establishment Pathway" – was completed in October 2005. This plan has been used to inform HHS as it considers contracts for egg-based facility expansion.
		Publication of the interim final rule titled, "Exceptions or Alternatives to Labeling Requirements for Products Held by the National Strategic Stockpile." ³⁹	FDA clearance of the SNS interim final rule occurred in November 2006. The rule is proceeding to HHS and OMB clearance.
	Explore scientific, legal and policy issues related to the use of veterinary vaccine facilities to increase human vaccine manufacturing capacity during an emergency.	Engage in discussions with USDA and other regulators regarding the feasibility of the use of veterinary vaccine facilities for human products.	Discussions with USDA occurred in January, March, and April 2006. At a WHO-sponsored meeting on April 27, 2006, USDA and FDA, as well as other foreign regulatory agencies and manufacturers, presented information on the use of veterinary facilities for manufacturing human influenza vaccines. Additional WHO-sponsored meetings have discussed a summary of issues pertaining to the use of veterinary facilities.
Work with industry, foreign public health authorities, and other stakeholders to assess preparedness and to develop strategies for harmonizing, where feasible, regulatory expectations for	Convene national regulatory authorities from around the world, under the aegis of the WHO, to work towards regulatory preparedness/convergence for pandemic influenza vaccines to maximize response preparedness in the event of an influenza pandemic.	FDA, as part of international working groups, will develop strategies and outline a framework of globally consistent regulatory approaches based on the available science.	Working group meetings are an ongoing activity
		Consensus documents	A WHO-affiliated meeting

<p>pandemic influenza vaccines to help increase the speed and efficiency of their development and production.</p>		<p>representing such an approach.</p>	<p>hosted by FDA, in Bethesda, Maryland, in June 2006, reviewed draft consensus documents and proposed a plan for the documents' availability in 2007.</p>
<p>Educate and exchange information with industry, foreign public health authorities, and other stakeholders on regulatory considerations.</p>	<p>Establish regular communications with foreign regulatory counterparts under our information sharing agreements.</p>	<p>Exchanges of information and collaboration on technologies and overcoming challenges.</p>	<p>Communications began in February 2006, and subsequent communications have occurred in May, July, and November 2006, and March 2007, with additional communications scheduled in 2007</p>
	<p>Conduct outreach regarding CGMPs and quality systems to encourage consistent and uninterrupted production of quality vaccines.</p>	<p>Presentations and interactions with industry and foreign counterparts on CGMP challenges.</p>	<p>This is an ongoing activity, with the next meeting scheduled for March 2007, in Barcelona, Spain, with an additional meeting scheduled for August 2007, in Cambridge, Maryland.</p>
		<p>Conduct a training workshop on CGMPs for foreign regulatory authorities to assist them in their efforts to ensure that CGMPs are applied to the manufacture of vaccines.</p>	<p>Training workshops will be held in the United States in May 2007.</p>
	<p>Exchange information with and educate vaccine manufacturers on regulatory considerations.</p>	<p>Organization of and participation in regular "Vaccine Roundtable" meetings.</p>	<p>Meetings are scheduled at regular intervals. The most recent meeting focused on selected topics, ranging from pre-approval through post-approval activities, and occurred in Fall 2006.</p>
<p>Work with the Office of the Secretary within HHS, CDC, the American Association of Blood Banks (AABB), and other organizations to develop responses to</p>	<p>Enhance existing regular communications and collaborative strategic activities focusing on pandemic influenza preparedness and responses within CBER and within HHS, CDC, and with industry organizations to ensure coordinated responses to emerging</p>	<p>Work with tissue and blood professional organizations and other stakeholders, including the AABB Interorganizational Task Force on Pandemic Influenza and the Blood</p>	<p>CBER actively serves as liaison participants in meetings with key stakeholders. Meetings have occurred in fiscal year 2006 and will continue in fiscal year 2007 to address the</p>

emerging potential threats to the safety and availability of blood, cell, and tissue products needed to support public health and medical care.	potential threats to blood, cell, and tissue safety and/or availability.	Supply, to assist their efforts to develop pandemic influenza planning strategies.	safety and availability of blood and tissue products to support public health and medical care.
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Table 2. Anti-Viral Drug Development, Production and Regulatory Review Subgroup: Pandemic Influenza Preparedness Objectives, Actions, Deliverables and Timeframes

Anti-Viral Drug Development, Production and Regulatory Review				
National Strategy Actions ⁴⁰	Objective	Action	Deliverable	Timeframe
6.1.6, 6.1.9, 6.1.13, 6.1.17, 6.3.5	Facilitate anti-viral drug development and regulatory review.	Evaluate and analyze initial pre-clinical data on drug safety, efficacy, and viral resistance from pre-IND, IND, and pre-EUA proposals and submissions. Refer potential sponsors in very early development to the National Institute for Allergy and Infectious Disease's (NIAID) drug screening program. Facilitate communications with sponsors using written responses, teleconferences, or face-to-face meetings, as appropriate to specific situations.	Reviews of pre-IND materials, INDs, and pre-EUA submissions.	Our goal is to complete reviews in reduced timeframes.
			Refer potential sponsors to the Web site for the NIAID drug screening program (www.niaid.nih.gov/dmid/viral).	We will refer potential sponsors to the Web site in response to inquiries.
			Advice and comments to sponsors via fax, letter, teleconference, or meeting, as appropriate, based on our review of the submitted material.	Our goal is to provide advice and comments to sponsors in a timely manner as appropriate to the submission's contents.
		Provide advice to industry and other Federal departments and agencies on clinical trial designs to evaluate the safety and efficacy of new anti-viral drug products or new formulations or dosing regimens of existing anti-viral drug products.	We will provide regulatory advice to industry and other Federal departments and agencies regarding the design of clinical trials of existing and new anti-viral drug products against influenza.	We have already reviewed several protocols in fiscal year 2006 and, as appropriate, have provided advice on development questions. Future timelines in fiscal year 2007 and beyond for the deliverables mentioned immediately above will be as appropriate to the
			Review of clinical trial protocols to test anti-viral drug products for safety and efficacy during the interpandemic period.	
			Advice and comment on	appropriate to the

		protocol design for multi-center and multi-national, randomized clinical trials.	submissions received. Our goal is to provide prompt responses.
	Review pre-EUA, IND, NDA, or BLA submissions and public or non-public information in support of potential uses of unapproved anti-viral drug products under an IND or EUA.	A Standard Operating Procedure (SOP) for issuing an EUA.	We will prepare a SOP in fiscal year 2007.
		Updates to our existing application tracking systems to accept pre-EUA submissions.	We will update the application tracking system by the first quarter of fiscal year 2008.
		Reviews of information from pre-EUA submissions, INDs, NDAs, and BLAs, and labeling, as appropriate.	<ul style="list-style-type: none"> We will expedite reviews as appropriate to the information submitted and the pandemic influenza phase.
	Provide information on our Web site (http://www.fda.gov/cder/ode4/preind/default.htm) to encourage early pre-IND interactions.	An updated Web site.	We have already posted updated contact information and links to drug label information. We will post additional updates as new information becomes available.
Expedite review of NDAs, BLAs, abbreviated new drug applications (ANDAs), and supplements for anti-viral drug products that may be relevant to preparedness for an	Prioritize pandemic influenza-related submissions in the Office of Generic Drugs (OGD), consistent with OGD review procedures	A template memorandum for expected ANDA submissions in anticipation of their receipt. (The memorandum would seek permission from the Director of CDER to raise the review priority in OGD.)	CDER prepared and cleared a template memorandum in fiscal year 2006.
	Employ expedited review mechanisms for NDAs, BLAs, ANDAs, and supplements, as appropriate.	Rapid completion of reviews and labeling.	We will complete reviews consistent with priority review or other available expedited review mechanisms.

<p>influenza pandemic.</p>	<p>Identify new targets for influenza viruses that may lead to identification of new classes of anti-viral drug products, and evaluate alternative drug development pathways, including the use of biomarkers and animal models that may expedite the availability of novel and promising anti-influenza therapies.</p> <p>Actively consider input from the scientific community by working with NIH/NIAID and participating in an expert panel on influenza to better understand the current challenges and opportunities in anti-viral drug development. The desired outcomes are:</p> <ul style="list-style-type: none"> • To help FDA in considering: <ul style="list-style-type: none"> ○ Whether there are animal models of influenza that will adequately predict human disease and responses; ○ Animal models studying novel viral strains to support and supplement clinical trial data in naturally occurring disease; ○ The relative contributions of studies in which volunteers have been exposed to weakened laboratory strains of virus to test the effects of anti-viral drugs (challenge studies) ; and ○ The appropriate design of clinical trials to maximize the efficient acquisition of data. • To support IND and EUA uses in emergency situations, as appropriate. 	<p>Participation in an NIH/NIAID expert panel.</p>	<p>An expert meeting, with invited FDA participation, was convened by NIH/NIAID in November 2006.</p>
	<p>Clarify the recommendations for pre-EUA submissions for pandemic influenza anti-viral drug products</p>	<p>A concept paper that provides recommendations on how an anti-viral drug product can be eligible for EUA and advice, on a case-by-case basis, in response to product-specific inquiries.</p>	<p>Active planning and initial drafting of the concept paper by the end of the second quarter of fiscal year 2007, with revisions as appropriate depending on the development of additional relevant information. We will provide advice in response to product-specific inquiries, as appropriate to inquiries received.</p>
	<p>Use scientific information from expert meetings, literature, etc., to identify and prioritize anti-</p>	<p>A list of issues with discussion points.</p>	<p>We included information from</p>

	influenza drug development issues.		literature articles in discussion of NIH/NIAID panel meeting plans during fiscal years 2006 and 2007. Monitoring of issues from the literature is an ongoing activity.
Facilitate product manufacturing and capability to address surge capacity.	Facilitate the expansion of domestic manufacturing capacity to produce anti-viral drugs against influenza.	Work with current manufacturers of anti-viral drug products to expand domestic production.	This is an ongoing activity with deliverables related to manufacturer-initiated submissions. Our goal is to complete reviews in reduced timeframes. Preliminary discussions of sublicensure proposals have taken place, and we will update them as appropriate to information becoming available. We have reviewed several manufacturing supplements already.
		Identification of possible mechanisms, if needed, to permit other manufacturers to produce proprietary anti-viral drug products, including discussion of sublicensure proposals from existing manufacturers.	
		Identification of alternate manufacturers capable of performing rate-limiting steps in manufacture.	
		Expedited inspections of new manufacturing sites.	
		Expedited review of information related to new manufacturing sites and manufacturing processes and controls.	
	Monitor drug supply issues and maintain a database of supply status and production capacity to enhance anticipation and assessment of shortages.	Updates on supply and shortage issues and our Critical Products Program database.	We have updated the Critical Products Program database in fiscal year 2006 and will update it, as appropriate, thereafter. We will provide updates on shortage issues as needed in response to reports of expected or actual shortage situations.
Active monitoring and passive	Work with HHS agencies to use existing surveillance systems, such as MedWatch, and develop post-emergency surveillance plans.	A post-emergency surveillance plan.	Active discussions during fiscal year 2007 for the

<p>surveillance of adverse events reported with anti-viral drug products used for pandemic influenza.</p>			<p>surveillance plan, with the plan's final form subject to revision as more information becomes available.</p>
		<p>Review of adverse event reports submitted to MedWatch associated with anti-viral drug products used for pandemic influenza.</p>	<p>Final review of influenza anti-viral drug adverse events from the 2005-2006 influenza season by fourth quarter of fiscal year 2007 and as appropriate to the level of the influenza season and reporting activity thereafter.</p>
		<p>Active monitoring for adverse events among patients presented for care in a network of emergency departments. This monitoring will occur through the existing National Electronic Injury Surveillance System Cooperative Adverse Drug Event Project maintained by CDC and FDA.</p>	<p>Monitoring adverse events is an ongoing activity.</p>
<p>Facilitate the deployment of stockpiled drugs in the event of an influenza pandemic.</p>	<p>Work with the CDC's Coordinating Office for Terrorism Preparedness & Emergency Response, Division of the Strategic National Stockpile (COTPER/DSNS) and industry, repackagers, and relabelers to facilitate advance development of packaging, labeling, and specialized instructions if there are requests to modify any of these for the purpose of addressing stockpile-specific storage or distribution issues for products which are in the stockpile or may be added to the stockpile. Respond to the CDC's COTPER/DSNS on the regulatory status of proposed novel packaging and labeling of anti-viral drug products. For example, new labeling may be necessary when investigational new drug products in the SNS are approved or licensed, or new, yet unapproved, packaging (such as unit of use or unit dose packaging) may be necessary in order to distribute a product effectively during a public</p>	<p>We have provided and will continue to provide a response or a plan of action to the CDC's COTPER/DSNS on inquiries regarding repackaging and relabeling.</p>	<p>During an influenza pandemic alert period, we will expedite the request for technical advice and provide a response no later than 60 days of receipt of the inquiry and as appropriate to the urgency of the matter.</p>
		<p>Priority review and action, as appropriate, on NDA supplements for packaging changes.</p>	<p>During an influenza pandemic alert period, we will review NDA supplements for packaging changes on a priority basis</p>

		health emergency.		as appropriate.
		Participate in an interagency working group to develop specific recommendations for anti-viral drug products to include in Federal and non-Federal stockpiles.	Technical advice on scientific and regulatory issues, as appropriate, during discussion and drafting of the recommendations.	We will provide advice within 60 days of its request.
		Work with the CDC's COTPER/DSNS to determine eligibility of future stockpiled products for the SLEP.	We will address requests from the CDC's COTPER/DSNS for the eligibility of future stockpiled products for participation in the SLEP.	We will address requests from the CDC's COTPER/DSNS for the eligibility of future stockpiled products for SLEP within 60 days.
			Work with SNS and SNS contractors to develop new expiry labeling to facilitate SLEP compliance.	We will respond to SNS and SNS contractors' requests to develop new expiry labeling within 60 days of a request.
		Consider expanding the existing SLEP beyond the Federal government.	A determination regarding the extension of SLEP beyond the Federal government.	The determination whether to extend SLEP was made first quarter of fiscal year 2007.
		Develop an after-action report addressing deployment of FDA- regulated products from the SNS.	A completed report pertaining to FDA-regulated products after the first wave of deployed product from the SNS.	Within 90 days after an event of such significance that it requires deployment of FDA-regulated products from the SNS.
		Coordinate with other Federal departments and agencies and State, local, and tribal public health departments that are developing plans to store anti-viral drug products at the SNS or at other designated sites and will be distributing anti-viral products through private distributors and/or other carriers to designated sites. FDA's input would be to help ensure proper conditions that comply with the product's labeled storage conditions.	Consultations with pharmaceutical manufacturers and distributors and with State, local, and tribal public health departments on possible storage facilities and storage requirements.	Fiscal year 2007.

Table 3. Device Development, Production and Regulatory Review Subgroup: Pandemic Influenza Preparedness Objectives, Actions, Deliverables and Timeframes

Device Development, Production, and Regulatory Review				
National	Objective	Action	Deliverable	Timeframe

Strategy Actions ⁴¹				
6.1.17, 6.2.1, 6.2.3	Facilitate development and regulatory review of influenza-related devices, including diagnostics and PPE devices.	Implement early interactions and communications with sponsors through face-to-face, pre-submission meetings and conference calls.	Expedited scheduling of meetings with sponsors.	This is an ongoing activity.
		Timely review and approval or clearance of devices.	Greater meeting opportunities for sponsors.	This is an ongoing activity
		Work with manufacturers to help ensure compliance with quality systems regulations (QSRs).	Expedite review of devices that may be needed for an influenza pandemic, as appropriate.	This is an ongoing activity.
		Work with manufacturers to help ensure compliance with quality systems regulations (QSRs).	Identification of device manufacturers with QSR issues that would or could affect safety and effectiveness. We will work with such manufacturers to address quality issues.	This is an ongoing activity.
			For those manufacturers with QSR issues, coordination and expedited scheduling and performance of inspections for PPE, influenza-related diagnostics, and other support devices such as ventilators, resuscitator bags, and endotracheal tubes.	This is an ongoing activity
Anticipate shortages and support efforts to prevent shortages of key devices.	Work with manufacturers to support efforts to ensure an adequate supply of diagnostics, PPE, and other devices that are expected to be in high demand during influenza outbreaks and for which short supplies are predicted.	Continuous liaisons with manufacturers and coordination with other HHS agencies or working groups to address medical products supply and availability.	Continuous liaisons with manufacturers and coordination with other HHS agencies or working groups is an ongoing activity.	Continuous liaisons with manufacturers and coordination with other HHS agencies or working groups is an ongoing activity.
		Updates to the list of the devices commonly used to manage influenza patients, including devices used for infection control. Identification of the devices that may be in short supply if demand increases.	Updates to the list of the devices commonly used to manage influenza patients, including devices used for infection control. Identification of the devices that may be in short supply if demand increases.	We prepared a list of devices in September 2006. Updating the list is an ongoing activity.
		Updated contact	Updated contact	We prepared contact

		information on manufacturer and the estimated number of select products available for immediate distribution, as well as the time that would be necessary to increase production to meet public health needs. We will verify the information every six months to ensure its accuracy.	information on manufacturers and the estimated number of select products in September 2006. Updating the contact information is an ongoing activity.
Ensure continued safety and effectiveness of influenza-related devices during the post-market phase of the product life-cycle.	Continue post-market monitoring and data analysis of adverse event reports on influenza-related devices to ensure the continued safety and effectiveness of marketed devices.	Prompt action on evidence of potential harm or increased risk to <ul style="list-style-type: none"> • users of these devices. 	This is an ongoing activity.
		Exchange of relevant information, as needed, with foreign regulatory authorities.	This is an ongoing activity.
		Continuous education of professionals and consumers on adverse event reporting mechanisms.	This is an ongoing activity.
	Require, as appropriate, post-market studies or information gathering on influenza-related devices. This can be accomplished in three different ways depending on the type of product involved and the applicable regulatory requirements. It may be required: (1) under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360I) and 21 CFR part 822, provided that the statutory and regulatory criteria are satisfied; (2) as a special control; or (3) as a condition of approval for class III devices. ⁴²	Work with manufacturers in the planning of post-market studies, as appropriate, and provide recommendations on the types of useful data to be collected in these studies.	We will provide recommendations within 60 days after receiving the premarket submission.

	Educate device users on how to use influenza-related devices in a safe and effective manner.	Develop educational materials on the uses of these devices, including appropriate warnings, precautions, and limitations.	Consultation with other agencies, such as CDC (including the National Institute for Occupational Safety and Health), the Occupational Safety and Health Administration (OSHA), and the Environmental Protection Agency (EPA), which may also provide advice regarding the selection and use of these devices, to ensure accurate and consistent messages	Consultation with other Federal departments and agencies is an ongoing activity.
			The posting of new informational material and the updating of existing material on our Web site.	Posting of new informational material occurred in June 2006 and September 2006. We will post updates as new information becomes available.
	Enhance communication with stakeholders.	Communicate FDA influenza-related device activities and information to industry, consumers, State, local, and tribal governments and other stakeholders. Collaborate with other Federal and international health agencies on public messages related to the use of influenza-related devices to ensure consistency and accuracy.	Influenza information on our Web site that is up-to-date and consistent with information disseminated by other Federal and international agencies.	This is an ongoing activity.

Table 4. Food and Feed Safety Subgroup: Pandemic Influenza Preparedness Objectives, Actions, Deliverables and Timeframes

Food and Feed Safety ⁴³				
National Strategy Actions ⁴⁴	Objective	Action	Deliverable	Timeframe
4.2.7, 4.3.6, 5.2.5,	Assess the likelihood of food and feed contamination with highly pathogenic avian and human	Monitor global avian influenza activity in wild and domestic avian	Stronger collaboration with and communication on influenza surveillance with	This is an ongoing activity.

<p>7.1.3, 7.3.1, 7.3.5</p>	<p>pandemic influenza virus.</p>	<p>species and pandemic influenza activity in humans to identify the potential for food and/or feed contamination.</p>	<p>CDC and USDA. Sharing of information with other Federal, State, local, and tribal government departments and agencies and international public health and animal health organizations.</p>	<p>This is an ongoing activity.</p>
		<p>Identify FDA-regulated foods (including dietary supplements) and animal feeds that are at elevated risk of contamination with infectious AI or pandemic influenza virus.</p>	<p>A list of FDA-regulated foods and feed ingredients that contain avian-derived materials.</p>	<p>Began in fiscal year 2006.</p>
		<p>Identify FDA-regulated foods (including dietary supplements) and animal feeds that are at elevated risk of contamination with infectious AI or pandemic influenza virus.</p>	<p>Identification of foods (in addition to whole shell eggs) that contain domestic or imported avian-derived ingredients.</p>	<p>Began in fiscal year 2006</p>
		<p>Identify FDA-regulated foods (including dietary supplements) and animal feeds that are at elevated risk of contamination with infectious AI or pandemic influenza virus.</p>	<p>A determination of the risk of contamination of food derived from marine and freshwater fish and shellfish from harvest waters that are potentially contaminated by infected waterfowl and domestic poultry.</p>	<p>Began in fiscal year 2006</p>
		<p>Identify FDA-regulated foods (including dietary supplements) and animal feeds that are at elevated risk of contamination with infectious AI or pandemic influenza virus.</p>	<p>An estimate of the likely level and frequency of contamination of ready-to-eat foods by infectious respiratory droplets from human cases of pandemic influenza.</p>	<p>Began in fiscal year 2006</p>
		<p>Investigate the effectiveness of food and feed processing and preparation practices for inactivating influenza viruses by:</p> <ul style="list-style-type: none"> • Determining typical food processing and preparation practices for FDA-regulated foods that contain eggs and avian tissues; • Conducting a literature search on the 	<p>Up-to-date information on conditions necessary in food and feed processing for the inactivation of influenza viruses.</p>	<p>Initial literature searches completed in fiscal year 2006, with additional data expected during fiscal years 2007 and 2008.</p>

		<p>survivability of influenza viruses in various conditions and in various food and feed matrices;</p> <ul style="list-style-type: none"> • Working with USDA's Agricultural Research Service (ARS) to determine the upper limits of virus titers in egg contents for various HPAI strains and time/temperature requirements for the inactivation of different HPAI strains in eggs and meat from game birds; • Communicating with the egg industry to determine temperatures achieved during different cooking methods for eggs; • Conducting in-house research on cooking and other processing methods to determine their effectiveness in inactivating influenza virus strains of interest in food; and • Collecting information on current procedures and practices used for the treatment of poultry litter intended for use in animal feed. 		
		<p>Develop analytical methods, reagents, and testing capability for identifying influenza virus in foods, as appropriate to protect the human food supply.</p>	<p>Publication of validated methods for detecting influenza virus in FDA-regulated foods.</p>	<p>Completed during fiscal years 2008 and 2009.</p>
		<p>In coordination with ORA, establish inspection plans for food and feed and, as</p>	<p>inspection plans for foods and feed.</p>	<p>Fiscal year 2008.</p>

	appropriate, sampling plans for foods based on the potential for contamination by AI viruses and availability of laboratory methods. Work with other Federal and State departments and agencies to enhance and increase the number of inspections of domestic products at elevated risk of contamination with AI viruses and imports from affected countries.	Sampling plans for analysis of potentially contaminated foods and, if identified, foods associated epidemiologically with human illness.	Fiscal year 2008.
Enhance communication with stakeholders.	Communicate our influenza-related food and feed safety activities and information to industry, consumers, State, local, and tribal governments, and other stakeholders. Collaborate with other Federal and international human/animal health departments and agencies on public messages related to AI and food and feed safety to ensure consistency and accuracy.	Influenza information on our Web site that is up-to-date and consistent with information disseminated by other Federal and international departments and agencies.	This is an ongoing activity. We will update the Web site on an as needed basis.
	Exchange with other Federal departments and agencies emerging data on the geographic distribution of AI strains of interest and of pandemic human strains, the tissue distribution of the AI virus, and the effects of factors important in food processing and preparation (e.g., temperature, pH, salt concentration) on inactivation of these viral strains.	Establishment of an information sharing forum with interagency membership, as appropriate.	We established the forum in fiscal year 2006.
	Enhance biosecurity measures for the food, feed, and rendering	"Best practices" guidance documents for the food, feed, and rendering	Fiscal year 2007.

	<p>industries to meet any additional risks posed by AI or an influenza pandemic. Work with industry, Federal, State, local and tribal departments and agencies, and others on biosecurity strategies. Identify and review existing biosecurity documents. Provide technical assistance to industry as it implements biosecurity measures. Work with USDA, EPA, and State, local, and tribal governments on disposal options for birds and potentially contaminated materials from infected flocks.</p>	<p>industries, as needed.</p>	
		<p>A final rule on shell egg <i>Salmonella Enteritidis</i> prevention.</p>	<p>Fiscal year 2007</p>
<p>Preserve the effectiveness and supply of drugs approved for the prophylaxis and treatment of influenza in humans.</p>	<p>Prohibit the extra-label use of human influenza anti-viral drug products in chickens, turkeys, and ducks.</p>	<p>An order prohibiting the extra-label use of influenza anti-viral drug</p> <ul style="list-style-type: none"> • products of the adamantane and <p>neuraminidase inhibitor drug classes in chickens, turkeys, and ducks.</p>	<p>We issued a final rule on March 22, 2006 in the <i>Federal Register</i> (71 FR 14374). The final rule became effective on June 20, 2006. We may expand the list of animal species affected as new data become available.</p>
	<p>Educate producers, veterinarians, the feed industry, and others about the public health threat posed by the use of human influenza anti-viral drug products in animals, and provide information about relevant prohibitions.</p>	<p>Collaboration with veterinary and producer organizations, international organizations, foreign governments, and others to disseminate information. This collaboration may take several forms, such as meetings, presentations to professional societies and to academia, and notifications to OIE</p>	<p>This is an ongoing activity.</p>

			member countries.	
		Provide testing capability for anti-influenza drug residues in avian-origin foods, as appropriate to protect the public health.	Validated analytical methods to detect and identify residues of influenza anti-viral drug products in the adamantane and neuramini-dase drug classes in poultry.	Fiscal year 2007-2008.
			Collaboration with the Central Science Laboratory ⁴⁵ of the United Kingdom's (U.K.'s) Department for Environment, Food and Rural Affairs (Defra) to develop and validate methods.	Fiscal year 2007-2008.
			Assistance in technology transfer to other public health laboratories.	Fiscal year 2007-2008.
		Enforce the final rule prohibiting the extra-label use of influenza anti-viral drugs in chickens, turkeys, and ducks. Assess the need for surveillance for human anti-influenza drug use in animals.	Surveillance plan and regulatory actions, as indicated.	This will be an ongoing activity.

Table 5. Emergency Preparedness, Response, and Communication Subgroup: Pandemic Influenza Preparedness Objectives, Actions, Deliverables and Timeframes

Emergency Preparedness, Response, and Communication				
National Strategy Actions ⁴⁶	Objective	Action	Deliverable	Timeframe
4.3.6, 6.1.1, 6.1.3, 6.1.4, 6.3.8	Ensure relevant agency operational and response plans are adequate for use if an influenza pandemic occurs and ensure these plans address the unique workplace situations an influenza pandemic would present compared to other	Integrate components from business recovery, continuity of government, continuity of operations, and disaster recovery plans into pandemic influenza plans as appropriate.	FDA Pandemic Influenza Emergency Response Plan (draft).	First quarter of fiscal year 2008 for the FDA Pandemic Influenza Emergency Response Plan draft.
			Submission of an FDA Operational Plan to the Department of Health and Human Services as an annex to the HHS	The FDA Operational Plan was submitted to the Department of Health and Human Services in December 2006, and was incorporated into Part II of the

	types of emergencies.		Pandemic Influenza Implementation Plan – Part II.	HHS Pandemic Influenza Implementation Plan.
			Exercise(s) to test the FDA Pandemic Influenza Emergency Response Plan and agency or center continuity of business operations plans.	Second quarter of fiscal year 2008 for the exercise(s).
	Inform our employees about our plans for maintaining business operations in the event of an influenza pandemic and provide updated information to our employees throughout the pandemic. Reassure our employees that we are attentive to their health, safety, and economic vitality.	Communicate with our employees about individual responsibility, mission travel, vaccine administration, anti-viral drug products, and work at home/shelter at home. Involve the National Treasury Employees Union, as appropriate, regarding significant changes in working conditions.	An established protocol for the use of electronic mail (e-mail) to inform employees.	We established a specific Office of Management Pandemic Influenza Preparedness Protocol on March 6, 2007, that provides regular electronic updates via e-mail, BlackBerry, and Internet Outlook Web Access. This protocol includes ongoing support with a recorded status line and call center response via phone or Intranet. Protocol services are supported by our Employee Resources and Information Center.
	Ensure we develop and issue FDA-specific public health messages and reports of our accomplishments in coordination with HHS and align with related HHS public health messages.	Coordinate with HHS expedited development and dissemination of public information.	A Strategic Communications Plan	Fiscal year 2007.
	Assess how we can use our inventories of FDA-regulated establishments that prepare, pack or hold commercially distributed drugs, biological products (including blood), devices, and feed if disruptions occur in the commercial shipment of such products.	Create subsets of FDA product line (i.e., drugs, biological products, etc.) inventories. From the inventory subsets, create geo-coded maps (maps in which geographic identifiers have been assigned) for identifying major industry sources that can respond if product shortages occur.	Up-to-date regional establishment lists and software upgrades and geo-coded maps of FDA-regulated establishments.	Geo-coded maps were created for all product subsets and provided to FDA field offices by the first quarter of fiscal year 2007. Updates to the maps will be provided on a monthly basis or sooner if needed. Additional software upgrades were made in the first quarter of fiscal year 2007 which will increase the speed and size of map development.
		Help OGHA and ASPR, Office of the Secretary (OS), HHS, to complete protocols of mutual	OS, under the Health Working Group of the Security and Prosperity Partnership of North	Provide technical input to OGHA and ASPR, in a timely manner in response to their requests, so as to contribute to

		assistance in the event of a cross-border emergency with Canada and Mexico.	America, has the lead for HHS. <ul style="list-style-type: none"> FDA will provide technical input to OS/HHS, on text for the protocol pertaining to the acceptance, in an emergency, of stockpiled drugs, vaccines, and medical supplies from the Canadian national stockpile. 	the OS/HHS deadline to complete the protocol by June 1, 2007.
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**Table 6. Enforcement Subgroup:
Pandemic Influenza Preparedness Objectives, Actions, Deliverables and Timeframes**

Enforcement				
National Strategy Actions ⁴⁷	Objective	Action	Deliverable	Timeframe
6.1.13	Investigate and pursue enforcement action against fraudulent or counterfeit products.	Use a risk-based approach to investigate reports of, and pursue enforcement action against, fraudulent or counterfeit products, particularly those that present a high risk to consumers.	Development of models to identify and prioritize targets.	Target selection and prioritization model in place by second quarter of fiscal year 2007.
			Removal of fraudulent and counterfeit products related to pandemic influenza and AI from the market.	Enforcement actions are an ongoing activity.
			Evaluation of enforcement activities and accomplishment reports.	Evaluation of enforcement activities and accomplishment reports will occur at least quarterly.
		In collaboration with the Department of Homeland Security (DHS), Department of Justice (DOJ), Department of State (DOS), and Department of Commerce (DOC), investigate and prosecute counterfeit drug cases and enforce	Investigation of reports of counterfeit drugs used for pandemic influenza treatment or for prophylactic purposes and prosecution of cases as evidence warrants.	This is an ongoing activity.

		Federal laws regarding counterfeit drugs, biological products, vaccines, devices, and other products used in a pandemic influenza situation.		
		In conjunction with DHS, DOJ, DOS, and DOC, institute an expanded plan for investigating and prosecuting cases involving counterfeit seasonal influenza drugs during an influenza pandemic. This includes development of a joint strategic plan for the detection, at the border, of international shipments of counterfeit vaccines and anti-viral drug products.	A joint strategic plan for interdicting or preventing international shipments of counterfeit vaccines and anti-viral drug products.	We will develop a draft plan by the third quarter of fiscal year 2007.
			Prevention or interdiction of international and domestic counterfeit drug shipments.	Prevention or interdiction of counterfeit drug shipments is an ongoing activity.
			Expansion of and updates to a plan of action to handle counterfeit drugs.	We will develop a draft plan of action to handle counterfeit drugs by the second quarter of fiscal year 2007.
			Filing of indictments for cases involving these counterfeit drugs.	Filing of indictments is an ongoing activity.
		Increase public awareness of fraudulent or counterfeit products relating to pandemic influenza and AI.	Press releases and public advisories.	We will issue press releases and public advisories as we take enforcement actions.
			Accomplishment reports.	We will prepare accomplishment reports at least quarterly.

Appendix: List of Abbreviations/Acronyms

AABB American Association of Blood Banks

AI Avian Influenza

ANDA Abbreviated New Drug Application

ARS Agricultural Research Service (USDA)

ASPR Office of the Assistant Secretary for Preparedness and Response, HHS

BLA Biologics License Application

CBER Center for Biologics Evaluation and Research, FDA

CDC Centers for Disease Control and Prevention

CDER Center for Drug Evaluation and Research, FDA

CDRH Center for Devices and Radiological Health, FDA

CFSAN Center for Food Safety and Applied Nutrition, FDA

CGMP Current Good Manufacturing Practices (also abbreviated as cGMP or sometimes as GMP)

COTPER/DSNS Coordinating Office for Terrorism Preparedness & Emergency Response, Division of the Strategic National Stockpile. (This is a CDC office.)

CVM Center for Veterinary Medicine, FDA

Defra Department for Environment, Food, and Rural Affairs (This is a department of the government of the United Kingdom.)

DHS Department of Homeland Security

DOC Department of Commerce

DOD Department of Defense

DOJ Department of Justice

DOS Department of State

EPA Environmental Protection Agency

EUA Emergency Use Authorization

FDA Food and Drug Administration

FR Federal Register

HHS Department of Health and Human Services

HPAI High Pathogenicity Avian Influenza

IND Investigational New Drug application

LPAI Low Pathogenicity Avian influenza

MDCK Madin-Darby canine kidney cells

MDUFMA Medical Device User Fee Modernization Act

NCTR National Center for Toxicological Research, FDA

NDA New Drug Application

NIAID National Institute for Allergy and Infectious Diseases, NIH

NIH National Institutes of Health

OCM Office of Crisis Management, FDA

OER Office of External Relations, FDA

OGC Office of the General Counsel, Food and Drug Division

OGD Office of Generic Drugs, CDER

OGHA Office of Global Health Affairs, HHS

OIE Organisation for Animal Health (formerly the Office International des Epizooties)

ORA Office of Regulatory Affairs, FDA

OS Office of the Secretary, HHS

OSHA Occupational Safety and Health Administration

PPE Personal Protective Equipment

QSR Quality Systems Regulations

SLEP Shelf-Life Extension Program

SNS Strategic National Stockpile

SOP Standard Operating Procedure

USA United States of America

USDA United States Department of Agriculture

VAERS Vaccine Adverse Events Reporting System

WHO World Health Organization

Glossary

Abbreviated New Drug Application – An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use.

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

The ANDA regulations are at 21 CFR part 314, subpart C.

Accelerated Approval - These regulations (and their corresponding statutory authority at section 112 of the Food and Drug Administration Modernization Act) allow FDA to approve products that provide a meaningful therapeutic benefit over existing therapies for serious or life threatening illnesses on the basis of an effect on a surrogate endpoint that FDA has determined is reasonably likely to predict clinical benefit. Accelerated approval is granted on the condition that the manufacturer must continue testing the drug in clinical trials to demonstrate that the drug indeed provides clinical benefit to the patient. If the studies fail to demonstrate clinical benefit of the drug, or if the sponsor does not pursue the confirmatory studies with due diligence, FDA may withdraw the product from the market more quickly than usual.

Current Good Manufacturing Practices - Manufacturers establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The quality systems for FDA-regulated products (food, drugs, biological products, and devices) are known as current good manufacturing practices (CGMP, also seen as cGMP or as GMP).

The CGMP regulations for food are at 21 CFR part 110. For human drugs and most biological products, the CGMP regulations are at 21 CFR parts 210 and 211. For devices, the CGMP regulations are at 21 CFR part 820 (quality system regulation).

Biologics License Application – Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The PHS Act requires a firm who manufactures a biological product for sale in interstate commerce to hold a license for the product. A biologics license application (BLA) is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical affects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product.

The BLA regulations are at 21 CFR part 601.

Emergency Use Authorization - Section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb-3) permits the Commissioner of Food and Drugs to authorize the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency involving a heightened risk of attack on the public or U.S. military forces. The Emergency Use Authorization (EUA) authority allows FDA to strengthen the public health protections against biological, chemical, radiological, and nuclear agents that may be used to attack the American people or United States armed forces. Under section 564 of the Act, the FDA Commissioner may allow medical countermeasures to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by such agents, when there are no adequate, approved, and available alternatives.

Investigational New Drug Application (IND) – Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are two general categories of INDs:

- **Commercial** – an IND for which the sponsor intends the product to be commercialized at some point. The sponsor for a commercial IND is generally a corporate entity or, in some cases, the National Institutes of Health or an academic institution.
- **Research (Non-Commercial)** – an IND for which a study is being conducted for research purposes rather than commercial development. These INDs are generally sponsored by an individual investigator or an academic institution.

Within the two IND categories, there are several IND types.

- "Standard IND," while not a regulatory term, refers to an IND submitted as described under 21 CFR 312.23. Such an IND could be either a commercial or research IND.
- [Emergency Use IND](#) is described in 21 CFR 312.36 and allows FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21 CFR 312.23 or 312.34. The sponsor is expected to make an appropriate IND submission as soon as practicable after authorization.
- [Treatment IND](#) is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted or while FDA review takes place. The treatment IND is described in 21 CFR 312.34.

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included is any previous experience with the drug in humans (often foreign use).
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials unless FDA grants a waiver. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

The IND regulations are at 21 CFR part 312.

New Drug Application (NDA) – The NDA is the vehicle through which drug sponsors formally propose that FDA approve a new pharmaceutical for sale and marketing in the United States. The data gathered during the animal studies and human clinical trials of an IND become part of the NDA.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged.

The NDA regulations are at 21 CFR part 314.

Quality Systems Regulations - The CGMP requirements set forth in the Quality System (QS) Regulation are promulgated under section 520 of the Act. They require that domestic or foreign manufacturers have a quality system for the design and production of medical devices intended for commercial distribution in the United States. The regulation requires that:

- various specifications and controls be established for devices;
- devices be designed under a quality system to meet these specifications;
- devices be manufactured under a quality system;
- finished devices meet these specifications;
- devices be correctly installed, checked and serviced;
- quality data be analyzed to identify and correct quality problems; and
- complaints are processed.

Thus, the QSR helps assure that medical devices are safe and effective for their intended use. FDA monitors device problem data and inspects the operations and records of device developers and manufacturers to determine compliance with CGMP requirements in the QSR (21 CFR part 820).

The QSR covers quality management and organization, device design, buildings, equipment, purchase and handling of components, production and process controls, packaging and labeling control, device evaluation, distribution, installation, complaint handling, servicing, and records.

Shelf Life Extension Program - The Department of Defense (DOD), Centers for Disease Control and Prevention (CDC), and Department of Veterans' Affairs (VA) maintain significant reserves of critical medical supplies. CDC maintains its reserves in the Strategic National Stockpile (SNS). These supplies include drug products, which have expiration dates. Constantly replacing drug products as they reach their expiration dates can be quite costly, so, to reduce overall costs to the Federal government and to the taxpayer, DOD, CDC, and VA work with FDA to determine whether a drug product's useful life can be extended beyond the expiration date. FDA tests samples submitted by participating Federal entities and analyzes the data to determine whether adequate supporting data are available to extend the expiration date of specified lots of stored drug products.

Strategic National Stockpile – The Strategic National Stockpile (SNS) is a national repository of antibiotics, chemical antidotes, antitoxins, life-support medications, IV administration, airway maintenance supplies, and medical/surgical items. The SNS is designed to supplement and re-supply state and local public health agencies in the event of a national emergency anywhere and at anytime within the United States or its territories.

Warning Letter - A warning letter is a written communication from FDA notifying an individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act, or other relevant statutes, and that failure of the responsible party to take appropriate and prompt action to correct and prevent any future repeat of the violation may result in administrative and/or regulatory enforcement action without further notice.

Footnotes

¹ Among influenza A viruses, there are 16 hemagglutinin and 9 neuraminidase subtypes, so viral subtypes are classified using the letters H and N.

² "National Strategy for Pandemic Influenza," Homeland Security Council, November 2005.

³ See "HHS Pandemic Influenza Plan," United States Department of Health and Human Services, dated November 2005, at page 4.

⁴ See "HHS Pandemic Influenza Plan," United States Department of Health and Human Services, dated November 2005, at page 16.

⁵ Among influenza A viruses, there are 16 hemagglutinin and 9 neuraminidase subtypes, so viral subtypes are classified using the letters H and N. Additionally, AI viruses are sometimes referred to as different forms: high pathogenicity avian influenza (HPAI) or low pathogenicity avian influenza (LPAI), based on their genetic composition and virulence for poultry. The strains of the H5N1 subtype currently causing widespread avian outbreaks are HPAI strains and are able to infect humans as well, although they have not shown an ability to transmit efficiently between humans as of the issue date of this plan. While much of the current pandemic

influenza discussions or plans refer to H5N1 because concerns that these outbreaks and sporadic human infections have the potential to result in pandemic influenza, other novel subtypes may have pandemic potential, and seasonally circulating subtypes are also important in generating information related to pandemic influenza preparedness. Therefore, our plan includes other subtypes that are relevant to pandemic influenza preparedness in many ways. For example, vaccines intended for use in seasonal influenza may contribute to pandemic influenza preparedness by establishing vaccine manufacturing and testing procedures that can be adapted readily to incorporate new antigens from a pandemic influenza strain.

⁶ See United States Department of Health and Human Services, "HHS Pandemic Influenza Plan," dated November 2005, at page 16.

⁷ World Health Organization Web site, http://www.who.int/csr/disease/avian_influenza/country/cases_table_2007_03_08/en/index.html, accessed on March 9, 2007.

⁸ "National Strategy for Pandemic Influenza," Homeland Security Council, November 2005.

⁹ "National Strategy for Pandemic Influenza: Implementation Plan," Homeland Security Council, May 2006, available on the Internet at http://www.whitehouse.gov/homeland/nspi_implementation.pdf, accessed on October 18, 2006.

¹⁰ "HHS Pandemic Influenza Plan," U.S. Department of Health and Human Services, November 2005, available on the Internet at <http://www.hhs.gov/pandemicflu/plan/pdf/HHSPandemicInfluenzaPlan.pdf>, accessed on October 18, 2006.

¹¹ "HHS Pandemic Influenza Implementation Plan – Part 1," U.S. Department of Health and Human Services, December 2006, available on the Internet at <http://www.hhs.gov/pandemicflu/implementationplan/>, accessed on December 18, 2006.

¹²A "rapid response team" consists of a small group of individuals or offices who possess a particular expertise and are assembled, usually for a limited time period, to address a specific problem or to perform a specific task. The problems or tasks are often priorities, but might not warrant the attention or involvement of a complete Task Force Subgroup.

¹³ RT-PCR stands for "Reverse Transcription – Polymerase Chain Reaction."

¹⁴ MDCK cells are an established cell line that is sometimes used as the host for the growth of attenuated viruses.

¹⁵ "National Strategy for Pandemic Influenza: Implementation Plan," Homeland Security Council, May 2006, at pages 31 through 32.

¹⁶ *Id.* at page 32.

¹⁷ *Id.* at pages 33 through 34.

¹⁸ "WHO Global Influenza Preparedness Plan," Department of Communicable Disease Surveillance and Response, Global Influenza Programme, World Health Organization, dated 2005, accessed on the Internet at www.who.int/csr/resources/publications/influenza/GIP_2005_5Eweb.pdf on February 14, 2006.

¹⁹ According to the WHO, "[t]he distinction between phase 1 and phase 2 is based on the risk of human infection or disease resulting from circulating strains in animals. The distinction is based on various factors and their relative importance according to current scientific knowledge. Factors may include pathogenicity in animals and humans, occurrence in domesticated animals and livestock or only in wildlife, whether the virus is enzootic or epizootic, geographically localized or widespread, and/or other scientific parameters."

²⁰ See note 17.

²¹ According to the WHO, "[t]he distinction between phase 3, phase 4, and phase 5 is based on an assessment of the risk of a pandemic. Various factors and their relative importance according to current scientific knowledge may be considered. Factors may include rate of transmission, geographical location and spread, severity of illness, presence of genes from human strains (if derived from an animal strain), and/or other scientific parameters."

²² See note 19.

²³ See note 19.

²⁴ Adjuvants are substances that help stimulate a body's development of immunity to a vaccine's ingredients; this bodily response helps make a vaccine more effective.

²⁵ In very basic terms, a "reassortant" is a viral strain that results from mixing two or more parental viral strains.

²⁶ In brief, the word "antisera" is the plural form of "antiserum," and an antiserum is defined as a serum containing an antibody or antibodies against specific antigens. (An antigen is a substance that is capable, under certain conditions, of inducing a specific immune response.) An antiserum provides immunity to a specific disease.

²⁷ This interim final rule will permit FDA to grant an exception or alternative to certain regulatory labeling provisions applicable to human drugs, biological products, or devices that are or will be included in the Strategic National Stockpile. Under the rule, the appropriate FDA Center Director will have the authority to grant an exception or alternative to such labeling requirements if he or she determines that compliance with such requirements could adversely affect the safety, effectiveness, or availability of specified lots, batches, or other units of human drugs, biological products, or devices that are or will be included in the SNS. A grant of an exception or alternative under the interim final rule will include any safeguards or conditions deemed appropriate by FDA to ensure that the labeling of such products includes information for the safe and effective use of the products given their anticipated circumstances of use. The interim final rule will facilitate the safety, effectiveness, and availability of appropriate medical countermeasures in the event of a public health emergency.

²⁸ Class III is the most stringent regulatory category for devices. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Class III devices are those that are intended for use in supporting or sustaining human life, are intended for a use of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury. Examples of Class III devices include high-frequency ventilators and needle destruction devices.

²⁹ The objectives and actions in part VI.D, focus on AI rather than pandemic influenza because most food and feed safety issues relate to potential pandemic strains that originate in birds rather than actual pandemic strains that are circulating in humans.

³⁰ A "felid" is a member of the cat family (*Felidae*), such as tigers, leopards, and domestic cats. The AI virus is known to have caused severe pneumonia in tigers and leopards who were fed infected poultry carcasses in a zoo (see Keawcharoen, J., et al., "Avian Influenza H5N1 in Tigers and Leopards," *Emerging Infectious Diseases* 10 (12): 2189-2191 (December 2004)). In March 2006, a domestic cat was found to be infected with the H5N1 virus; the cat was found in an area where infected birds had been found (see OIE, "Avian Influenza in Cat in Germany," Press Release dated 01 March 2006). Domestic cats have been infected experimentally by contaminated food and shed large amounts of virus in their feces, which makes fecal-oral transmission possible in this species (see Rimmelzwaan, G.F., et al., "Influenza A Virus (H5N1) Infection in Cats Causes Systemic Disease with Potential Novel Routes of Virus Spread Within and Between Hosts," *American Journal of Pathology* 168: 176-183 (January 2006)).

³¹ The Central Science Laboratory provides research, scientific services, and support to Defra, other U.K. government departments, and the private sector.

³² We discuss communication with manufacturers, other Federal departments and agencies, foreign governments, public health organizations, and other entities elsewhere throughout this plan.

³³ "Talk Papers" are documents that guide our staff in responding consistently and accurately to public questions on subjects of current interest. Although we do not issue Talk Papers to the public, the information within a Talk Paper is publicly releasable.

³⁴ Food and Drug Administration, "FDA Acts to Protect Public from Fraudulent Avian Flu Therapies," dated December 13, 2005, available on the internet at www.fda.gov/bbs/topics/NEWS/2005/NEW01274.html, accessed on March 3, 2006.

³⁵ Food and Drug Administration, "FDA Statement on Fraudulent, Unapproved Influenza-Related Products," dated January 20, 2006, available on the internet at www.fda.gov/bbs/topics/NEWS/2006/NEW01301.html, accessed on March 3, 2006.

³⁶ Actions taken from the National Strategy for Pandemic Influenza: Implementation Plan, available on the internet at www.whitehouse.gov/homeland/pandemic-influenza-implementation.html, accessed on July 26, 2006.

³⁷ In very basic terms, a "reassortant" is a viral strain that results from mixing two or more parental viral strains.

³⁸ In brief, the word "antisera" is the plural form of "antiserum," and an antiserum is defined as a serum containing an antibody or antibodies against specific antigens. (An antigen is a substance that is capable, under certain conditions, of inducing a specific immune response.) An antiserum provides immunity to a specific disease.

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⁴⁰ Actions taken from the National Strategy for Pandemic Influenza: Implementation Plan, available on the internet at

www.whitehouse.gov/homeland/pandemic-influenza-implementation.html, accessed on July 26, 2006.

⁴¹ Actions taken from the National Strategy for Pandemic Influenza: Implementation Plan, available on the internet at www.whitehouse.gov/homeland/pandemic-influenza-implementation.html, accessed on July 26, 2006.

⁴² Class III is the most stringent regulatory category for devices. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Class III devices are those that are intended for use in supporting or sustaining human life, are intended for a use of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury. Examples of class III devices include high frequency ventilators and needle destruction devices.

⁴³The objectives and actions under Food and Feed Safety focus on AI rather than pandemic influenza because most food and feed safety issues relate to potential pandemic strains that originate in birds rather than actual pandemic strains that are circulating in humans.

⁴⁴ Actions taken from the National Strategy for Pandemic Influenza: Implementation Plan, available on the internet at www.whitehouse.gov/homeland/pandemic-influenza-implementation.html, accessed on July 26, 2006.

⁴⁵ The Central Science Laboratory provides research, scientific services, and support to Defra, other U.K. government departments, and the private sector.

⁴⁶ Actions taken from the National Strategy for Pandemic Influenza: Implementation Plan, available on the internet at www.whitehouse.gov/homeland/pandemic-influenza-implementation.html, accessed on July 26, 2006.

⁴⁷ Actions taken from the National Strategy for Pandemic Influenza: Implementation Plan, available on the internet at www.whitehouse.gov/homeland/pandemic-influenza-implementation.html, accessed on July 26, 2006.

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