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CHAPTER 5: VACCINES

Introduction

Vaccination offers one of the most effective measures for minimizing the morbidity and mortality related to influenza virus infection. Annual influenza vaccination has been the primary method by which the disease burden of seasonal influenza epidemics has been reduced in the United States and globally.

An influenza pandemic, however, will challenge public health officials to make critical decisions about vaccine use and distribution beyond what is routinely done for seasonal influenza. Decisions need to be made prior to a pandemic and, accordingly, HHS has already begun to undertake efforts to facilitate critical vaccine-manufacturing capacity building and rapid implementation of pandemic influenza vaccination. Vaccines produced for pandemic influenza prevention must be safe, readily produced in large quantities, and delivered quickly, and must protect the largest number of individuals possible. The rapid production and clinical evaluation of investigational lots of pandemic vaccines must be a top priority for the United States and the global public health community. This chapter describes specific HHS actions on pandemic vaccine research, development, manufacturing infrastructure building, preparedness, and response for vaccine usage.

Before a vaccine against the circulating pandemic virus strain becomes available, pre-pandemic vaccine from stockpiles (if closely matched to the circulating virus) may be made available to persons in designated priority groups. Once a well-matched vaccine against the circulating pandemic virus strain becomes available, its distribution and use will become a major focus of pandemic response efforts.

The primary areas of concern for vaccines relative to pandemic planning and response include the following:

- Selection of pre-pandemic influenza virus isolates for vaccine development
- Applicability and linkage of vaccine development and clinical evaluation projects for pandemic vaccine candidates to prepare vaccine stockpiles for pandemics
- Availability of influenza virus reference strains for vaccine manufacturing
- Domestic surge capacity for influenza vaccine manufacturing of pre-pandemic vaccine stockpiles and well-matched pandemic vaccines
- Regulatory review processes for the utilization of and acceptance of pre-pandemic and pandemic vaccines
- Utility of mismatched pre-pandemic vaccines at the precipice of pandemics
- Positioning of pre-pandemic and pandemic vaccines for distribution

- Funding sources and procurement mechanisms that include liability immunity for pre-pandemic and pandemic vaccine manufacture
- Vaccine safety and efficacy
- Mechanisms for deployment of pre-pandemic and pandemic vaccines from stockpiles
- Communication of messages about vaccines during pre-pandemic and pandemic periods

The scenarios covered by this implementation plan on pandemic vaccines include preparations for and actions during pre-pandemic and pandemic phases.

Role of HHS in Vaccines

The role of HHS with respect to vaccines is to facilitate the development, production, distribution, and utilization of pre-pandemic and pandemic vaccines. Specifically, HHS will:

- Establish and maintain sufficient stockpiles (~ 40 million doses) of pre-pandemic influenza vaccine—obtained from U.S.-licensed influenza vaccine manufacturers—against circulating influenza virus with pandemic potential without interrupting seasonal influenza vaccine manufacturing during pre-pandemic periods
- Expand seasonal influenza domestic vaccine production (to cover the U.S. population for whom vaccine is recommended) through normal commercial markets
- Develop virus reference strains from human clinical isolates, and qualify and ship them from HHS and WHO-collaborating virus reference laboratories to designated U.S.-licensed influenza vaccine manufacturers for vaccine development and manufacturing
- Work, in concert with Federal partners and the pharmaceutical industry, to expand and diversify domestic vaccine-manufacturing surge capacity sufficient to produce vaccine for the entire U.S. population (~ 300 million persons) within 6 months of the start of a pandemic
- Work with pharmaceutical industry and FDA to expedite the production and testing of virus reference antigen and serum reagents for vaccine potency assays
- Complete priority group planning and revise priorities periodically during a pandemic as warranted
- Work, in concert with Federal partners, with the pharmaceutical industry to procure vaccine directed against the pandemic strain and to distribute vaccine to

State, local, and tribal public health authorities for predetermined priority groups based on preapproved State plans

- Provide a well-matched pandemic vaccine within 6 months of the start of a pandemic for *pro rata* allocation of pandemic vaccine as available to the States for distribution to the 300 million people
- Provide a physical security plan for domestic influenza manufacturing and distribution facilities
- Promote the linkage between influenza surveillance and vaccine development
- Encourage the monitoring for and reporting of post-vaccine-administration adverse events to ensure safety and indicate trends
- Encourage usage of pneumococcal vaccine, especially in elderly populations, prior to and during an influenza pandemic
- Distribute vaccine according to the prioritization schedule outlined in the "HHS Pandemic Influenza Plan" to prevent disease and virus spread and to provide continuity of a constitutional government and maintain social and economic order
- Evaluate vaccine safety and efficacy

Specific Assumptions and Planning Considerations for HHS on Vaccine Issues

- As susceptibility to the pandemic influenza subtype will be universal, all persons should have the opportunity for vaccination during a pandemic.
- Indemnification will be considered for non-U.S. Government suppliers of pre-pandemic and pandemic influenza virus reference strains and U.S. pandemic influenza vaccine manufacturers.
- Antigenic drifts or new clades of pre-pandemic influenza viruses will require the continual production of working virus seeds for vaccine production and vaccine candidates for clinical evaluation for safety, antigenic dosing, and immunogenicity.
- Although pre-pandemic vaccines may not be well matched to pandemic viruses and may not provide complete protection, stockpiles of pre-pandemic vaccines that exhibit cross-clade protection and/or virus neutralization should provide limited and life-saving immunity to healthy critical workforce persons.
- A HHS pre-pandemic influenza vaccine stockpile should be of sufficient size to immunize up to 20 million persons (U.S. military, critical government workforce, and critical infrastructure and medical workforces).
- The provision of adequate security will be required to protect vaccine components and stocks during manufacturing, shipping, and storage, and at administration sites.

HHS Actions and Expectations

Pillar One: Preparedness and Communication

HHS facilitation and support for the research and development of an influenza pandemic vaccine encompasses influenza vaccine type, component, and delivery development, evaluation, and production; refinement of vaccination protocols; and enhancement of vaccine manufacturing and government policies for expanding vaccine manufacturing surge capacities. It also includes the establishment and testing of vaccine distribution and monitoring networks. Inherent in this HHS effort and support is the concomitant building of resources needed for regulatory advice and vaccine production oversight.

Pillar One components of HHS actions listed in this chapter are intended to integrate HSC actions and expectations concerning pandemic vaccines into a comprehensive package for influenza vaccine research and development (HSC 6.1.16, 6.1.17), domestic commercial scale vaccine production (HSC 6.1.7, 6.1.8, 6.1.10), pre-pandemic vaccine stockpiling (HSC 4.1.5, 6.1.7, 6.1.14), pandemic vaccine surge capacity building (HSC 6.1.16), and vaccine distribution and monitoring (HSC 6.1.6, 6.1.13, 6.1.16, 6.1.13, 6.3.5). Communication of HHS vaccine recommendations is also embodied in these actions (HSC 6.1.12). These actions cover HHS provisions for Federal advice and oversight of vaccine production (HSC 6.1.11) and usage (HSC 6.1.13, 6.1.13, 6.1.14).

Advancing Scientific Knowledge and Accelerating Development

A. Action (HSC 6.1.17.1): HHS will continue to support the development and clinical evaluation of novel vaccines and vaccination strategies (e.g., adjuvants, alternative delivery systems, common epitope vaccines).

   Timeframe: 12 months.

   Measure of Performance: Research grants and/or contracts awarded to support the development of influenza vaccines (including polyvalent influenza vaccines), adjuvants and dose-sparing strategies, and more efficient delivery systems, leading to initiation of phase I and II clinical trials to evaluate influenza vaccines and vaccination strategies.

   Step 1: Fund manufacturers for production of new vaccines to study and answer questions about vaccine dose schedule.

   Step 2: Prepare, acquire, and provide access to virus reference strains representative of target influenza viruses.

   Step 3: Provide advice, and advise on manufacturing issues.

Step 4: Stimulate and coordinate development of adjuvant vaccines and other immune-enhancing and antigen-sparing approaches.

Step 5: Engage in Cooperative Research and Development Agreement (CRADA) with academia and industry to facilitate vaccine development (e.g., CRADA between the Laboratory of Infectious Diseases [LID], National Institute of Allergy and Infectious Disease [NIAID], and MedImmune on the development of live, attenuated pandemic vaccine reference strains).

Step 6: Award contracts for advanced development of cell-based influenza vaccines to enhance and enlarge domestic pandemic vaccine manufacturing capacity.

Step 7: Provide contracts for advanced development of pandemic influenza vaccines that afford enhanced immunity (e.g., stimulated protective immunity, fewer doses) and/or doses-sparing effects (e.g., less antigen in vaccine) using live, attenuated influenza vaccines, adjuvants, immunostimulants, immune cytokines, or medical devices toward U.S. licensure.

Step 8: Provide contracts for advanced development of "universal" influenza vaccines that may provide cross-protective immunity against influenza subtype and strains toward U.S. licensure. The vaccines are expected to be targeted against conserved influenza M2 proteins or peptides and other viral and/or host proteins.

B. Action (HSC 6.1.16.1): HHS will continue to support the advanced development of cell-culture based influenza vaccine candidates.

Timeframe: Within 6 months.

Measure of Performance: Research grants and/or contracts awarded to develop cell-culture based influenza vaccines against currently circulating influenza strains with pandemic potential.

Step 1: Provide support and advice for new manufacturers interested in producing influenza virus vaccines.

Step 2: Provide support and advice for current manufacturers interested in expanding capabilities for preparation of influenza virus vaccines.

Step 3: Provide support for advanced development of improved and new vaccine technologies, vaccine acquisition, and vaccine manufacturing facility construction.

C. Action (HSC 4.1.6.2): HHS, in coordination with the WHO Secretariat, will establish at least six new sites for Collaborative Clinical Research on Emerging Infectious Diseases to conduct collaborative clinical research on therapeutics and the natural history of avian influenza. In addition, HHS will provide in-country support for one or more partner countries for human avian influenza clinical trials. (Also see chapter 1, Pillar One, Actions R and S [HSC 4.1.6.1 and 4.1.6.2] and chapter 6, Pillar One, Action E [HSC 4.1.6.2].)

Timeframe: 18 months.

Measure of Performance: Cooperative programs established in six new sites, to include the initiation of research and design of clinical trials.

Step 1: Develop clinical protocols for implementation to evaluate the safety and immunogenicity of pandemic vaccine candidates during the interpandemic period.

Step 2: Develop clinical protocols for implementation to evaluate the safety and immunogenicity of pandemic vaccine candidates during the pandemic period.

Step 3: Establish new clinical sites overseas for pandemic vaccine and therapeutics clinical evaluation and provide technical assistance in the development of in-country vaccine and therapeutic development for pandemic influenza.

D. Action (HSC 6.1.17.4): HHS will increase access to standardized influenza reagents for use in influenza tests and research. (Also see chapter 2, Pillar One, Action G [HSC 6.1.17.4].)

Timeframe: Within 6 months.

Measure of Performance: Standardized influenza reagents distributed to domestic and international partners within three (3) business days of a request.

Step 1: Prepare and characterize virus reference strain reassortants of influenza viruses with pandemic potential for vaccine development to support laboratory research, clinical studies, and vaccine manufacturing.

Step 2: Prepare and characterize reagents (e.g., virus reference antigens, virus reference antiserum) for standardization of vaccines for strains with pandemic potential to support laboratory and clinical studies and manufacturing.

E. Action (HSC 6.1.15.3): HHS will develop protocols and procedures to ensure timely reporting to Federal agencies and submission for publication of data from HHS-supported influenza vaccine evaluation studies. (Also see chapter 2, Pillar

One, Action Q [HSC 6.1.15.3] and chapter 6, Pillar One, Action D [HSC 6.1.15.3].)

Timeframe: Within 6 months.

Measure of Performance: Data shared within one (1) month of analysis or publication of completed clinical trial study.

Step 1: Prepare procedures and plans to select and secure appropriate data from HHS-supported influenza vaccine evaluation studies.

Step 2: Prepare database with previously reported pandemic information from clinical trials and other research venues.

Manufacturing Vaccines

F. Action (HSC 6.1.8.1): HHS will work with the pharmaceutical industry toward the goal of developing domestic vaccine production capacity sufficient to provide vaccine for the entire U.S. population within 6 months after the development of a vaccine reference strain.

Timeframe: 60 months.

Measure of Performance: Domestic vaccine manufacturing capacity in place to produce 300 million courses of vaccine within 6 months of development of a vaccine reference strain during a pandemic.

Step 1: Secure raw materials and other vaccine-related supplies.

Step 2: Award contracts for acquisition of domestically-manufactured pandemic vaccines based on pandemic virus strain, vaccine type and efficacy, stage of vaccine development, and vaccine availability.

G. Action (HSC 6.1.10.1): HHS, in coordination with the private sector, will assess the ability of U.S.-based pharmaceutical manufacturing facilities to contribute surge capacity and to retrofit existing facilities for pandemic vaccine production.

Timeframe: 6 months.

Measure of Performance: Completed assessment.

Step 1: Assess facility capacities in private sector to support vaccine manufacturing through requests for information and other fact-finding mechanisms.

- Expanded egg-based influenza vaccine manufacturing facilities

- New cell-based influenza vaccine manufacturing facilities
- Retrofitting of existing domestic FDA-licensed vaccine and biologics manufacturing facilities.

Step 2: Make recommendations to policymakers for request of contracts to build capacity.

H. Action (HSC 6.1.16.2): HHS will support the renovation of existing U.S. manufacturing facilities that produce other FDA-licensed cell-based vaccines or biologics and the establishment of new domestic cell-based influenza vaccine manufacturing facilities. (Also see Pillar One, Action G [HSC 6.1.10.1] above.)

Timeframe: 36 months.

Measure of Performance: Contracts awarded for renovation or establishment of domestic-cell based influenza vaccine manufacturing capacity.

Step 1: Make request for proposals to develop and/or acquire pandemic vaccines and provide assistance in the building of necessary capacity.

Step 2: Award contracts leading to the establishment and maintenance of adequate domestic pre-pandemic and pandemic vaccine manufacturing capacity.

I. Action (HSC 6.1.11.1): HHS will assess its existing authorities and develop a plan of action to address any regulatory or other legal issues related to the expansion of domestic vaccine production capacity.

Timeframe: 12 months.

Measure of Performance: Regulatory and legal issues identified in assessment.

Step 1: Determine indemnification issues for manufacturing and usage of pandemic vaccines.

Step 2: Determine intellectual property issues for pandemic vaccine manufacturing.

J. Action (HSC 6.1.11.2): HHS will develop a protocol and decision tools to implement liability protections and compensation, as authorized by the Public Readiness and Emergency Preparedness Act (P.L. 109–148).

Timeframe: 6 months.

Measure of Performance: Publication of protocol and decision tools.

Step 1: Determine product liability relief issues for manufacturing and usage of pre-pandemic and pandemic vaccines and develop advice for usage of Public Readiness and Emergency Preparedness (PREP) Act (P.L. 109–148).

Step 2: Prepare draft declarations for pre-pandemic and pandemic scenarios.

Step 3. Prepare operational protocol and agreements with interdepartmental partners (i.e., Departments of Justice and Treasury) for utilization of PREP Act for liability immunity.

K. Action (HSC 6.1.10.2): HHS, in coordination with DHS, DOD, VA, DOC, DOJ, and Treasury, will assess whether use of the Defense Production Act or other authorities would provide sustained advantages in procuring medical countermeasures.

Timeframe: Within 6 months.

Measure of Performance: Analytical report completed on the advantages/disadvantages of invoking the Defense Production Act to facilitate medical countermeasure production and procurement.

Step 1: Determine whether usage of the Defense Production Act or other authorities facilitates the procurement of pandemic countermeasures.

Step 2: Prepare draft options paper for consideration using different pre-pandemic and pandemic scenarios.

Prioritizing, Stockpiling, and Storing Vaccines

L. Action (HSC 6.1.7.1): HHS, in coordination with DHS, DOJ, and VA, in collaboration with State, local, and tribal partners, will determine the national medical countermeasure requirements to ensure the sustained functioning of medical, emergency response, and other front-line organizations. (Also see chapter 8, Pillar One, Action W [HSC 6.1.7.1].)

Timeframe: Within 12 months.

Measure of Performance: More specific definition of sectors and personnel for priority access to medical countermeasures and quantities needed to protect those groups; advice provided to State, local, and tribal governments and to infrastructure sectors for various scenarios of pandemic severity and medical countermeasure supply.

Step 1: Collect recommendations from interdepartmental working group on mechanisms to provide options and recommendations to policymakers on pre-pandemic and pandemic vaccine prioritization.

Step 2: Disseminate priority and subpriority vaccination guidelines through public and private sector partners (Association of State and Territorial Health Officials [ASTHO], NACCHO, CSTE, Association of Immunization Managers [AIM], AMA, ACP, American Academy of Pediatrics [AAP], American Association of Family Practitioners [AAFP], American Nurses Association (ANA), and National Influenza Vaccine Summit).

M. Action (HSC 6.1.7.2): HHS will establish and maintain stockpiles of pre-pandemic vaccines adequate to immunize at least 20 million persons against influenza strains that present a pandemic threat, as soon as possible within the constraints of industrial capacity. (Also see Pillar One, Actions G, K, I, and H [HSC 6.1.10.1, 6.1.10.2, 6.1.11.1, and 6.1.16.2] above.)

Timeframe: As soon as possible.

Measure of Performance: Procurement of 20 million courses of pre-pandemic vaccine against influenza strains presenting a pandemic threat.

Step 1: Assess needs within 6 months and secure raw materials and other vaccine-related supplies.

Step 2: Award contracts for acquisition of pre-pandemic vaccines based on virus strain, vaccine type, stage of vaccine development, vaccine stockpile inventory, vaccine stability, and pandemic potential.

Step 3: Within 6 months, determine product liability relief issues for manufacturing and usage of pre-pandemic vaccines and develop advice for usage of Public Readiness and Emergency Preparedness Act (P.L. 109–148).

Step 4: Facilitate domestic pandemic vaccine surge capacity building.

Step 5: Determine whether usage of the Defense Production Act or other authorities facilitates the procurement of pandemic countermeasures.

N. Action (HSC 4.1.5.3): HHS will provide technical expertise, information and guidelines for stockpiling and use of pandemic influenza vaccines. (Also see chapter 1, Pillar One, Actions Q and R [HSC 4.1.5.3 and 4.1.6.1].)

Timeframe: 6 months.

Measure of Performance: All priority countries and partner organizations have received relevant information on influenza vaccines and application strategies.

Step 1: Assess needs with interagency panel against WHO criteria and U.S. global vaccine resources and technical expertise.

Step 2: Determine best ways to assist with available local and regional vaccine manufacturing resources.

Step 3: Provide assistance with WHO advice and in collaboration with regional partners consistent with cultural sensitivities.

Distribution of Vaccines

O. Action (HSC 6.1.13.5): HHS, in coordination with DHS, DOS, DOD, DOL, VA, and in collaboration with State, local, and tribal governments and private sector partners, will develop plans for the allocation, distribution, and administration of pre-pandemic vaccine. (Also see chapter 8, Pillar One, Action BB [HSC 6.1.13.5].)

Timeframe: Within 9 months.

Measure of Performance: Department plans developed and advice disseminated to State, local, and tribal authorities to facilitate development of pandemic response plans.

Step 1: Develop prioritization guidelines for allocation of pre-pandemic vaccine prior to and at the onset of a pandemic.

Step 2: Develop distribution guidelines for federally purchased pre-pandemic vaccine; guidelines must include standard commercial distribution contractors for vaccines and integrated plan for physical security measures of vaccine manufacturing facilities, distribution centers, critical suppliers, and transportation routes by multilevel law enforcement team.

Step 3: Contract distribution of pandemic vaccine with private sector distributors and other carriers.

Step 4: Institute prescribed physical security measures for vaccine manufacturing, storage, and distribution centers, critical suppliers, and transportation routes using a preset pandemic plan and multilevel law enforcement team.

P. Action (HSC 6.1.13.1): HHS, in coordination with DHS, DOD, VA, and DOJ, and in collaboration with State, local, and tribal partners and the private sector, will work to ensure that States, localities, and tribal entities have developed and exercised pandemic influenza countermeasure distribution plans, and can enact security protocols if necessary, according to pre-determined priorities. (Also see chapter 6, Pillar One, Action Q [HSC 6.1.13.1]; and chapter 8, Pillar One, Action X [HSC 6.1.13.1].)

Timeframe: Within 12 months.

Measures of performance: Ability to activate, deploy, and begin distributing contents of medical stockpiles in localities as needed, established and validated through exercises.

Step 1: Determine capabilities needed for implementation, and develop vaccine delivery plan.

Step 2: Provide training for vaccine delivery through exercises.

Q. Action (HSC 6.1.14.1): HHS, in coordination with DHS and Sector-Specific Agencies, DOS, DOD, DOJ, DOL, VA, Treasury, and State/local governments, will develop objectives for the use of, and strategy for allocating, vaccine stockpiles during pre-pandemic and pandemic periods under varying conditions of countermeasure supply and pandemic severity. (Also see Pillar One, Action T [HSC 6.1.13.9] below; chapter 2, Pillar Three, Actions C [No HSC number] and D [HSC 6.1.13.9]; and chapter 6, Pillar One, Action C [6.1.14.1].)

Timeframe: Within 3 months.

Measure of Performance: Clearly stated objectives for vaccine usage under different scenarios including vaccine supply and pandemic severity.

Step 1: Review existing principles and assumptions guiding the allocation plans for pre-pandemic and pandemic vaccines.

Step 2: Provide revisions to these principles and assumptions to these allocation plans and present to working groups making recommendations to policymakers.

R. Action (HSC 6.1.14.2): HHS, in coordination with DHS and Sector-Specific Agencies, DOS, DOD, DOL, VA, Treasury, and State/local governments, will identify lists of personnel and high-risk groups who should be considered for priority access to medical countermeasures, under various pandemic scenarios, according to strategy developed in compliance with HSC 6.1.14.1. (Also see chapter 6, Pillar One, Action N [HSC 6.1.14.2].)

Timeframe: Within 9 months.

Measure of Performance: Provisional recommendations of groups who should receive priority access to vaccines established for various scenarios of pandemic severity and medical countermeasure supply.

Step 1: Review existing allocation plans for pre-pandemic and pandemic vaccines.

Step 2: Provide options paper on revisions to these allocation plans and present to policymakers for consideration.

S. Action (HSC 6.1.14.3): HHS, in coordination with DHS and Sector-Specific Agencies, DOS, DOD, DOL, and VA, will establish a strategy for shifting priorities based on at-risk populations, supplies and efficacy of countermeasures against the circulating pandemic strain, and characteristics of the virus.

Timeframe: Within 9 months.

Measure of Performance: Clearly stated process for evaluation and adjustment of prepandemic recommendations regarding groups receiving prior access to vaccines.

Step 1: Review pandemic vaccination priority guidelines to divide priority groups into subgroups if possible. Given pandemic influenza vaccine may become available only over a long period of time, developing smaller priority groups appears necessary.

Step 2: Develop guidelines for estimating priority group size, to ensure consistency across States and facilitate equitable vaccine distribution and critical infrastructure workforce needs.

Step 3: Disseminate priority and subpriority vaccination guidelines through public and private sector partners.

Step 4: Establish a strategy for adjusting priorities during the course of a pandemic based on the features of the pandemic strain.

Monitoring Vaccine Efficacy, Coverage, and Adverse Events

T. Action (HSC 6.1.13.9): HHS, in coordination with DOD, and VA, in collaboration with State, territorial , tribal, and local partners, will develop/refine mechanisms to (1) track adverse events following vaccine administration; (2) ensure that individuals obtain additional doses of vaccine, if necessary; and (3) define protocols for conducting vaccine effectiveness studies during a pandemic. (Also see chapter 2, Pillar Three, Action D [HSC 6.1.13.9]; and chapter 6, Pillar Three, Action C [HSC6.1.13.9].)

Timeframe: Within 18 months.

Measure of Performance: Mechanism(s) to track vaccine coverage and adverse events.

Step 1: Develop guidelines for vaccine accountability and reporting, consistent with HHS/CDC's Vaccine Management Business Improvement Project.

Step 2: Define parameters for tracking system(s) of vaccine recipients, including common variables that can be used in State-based systems and reported to HHS/CDC. This system will allow monitoring of trends and progress of the pandemic vaccination program and the appropriateness of vaccine use, and will identify problems in vaccine use to target for remedial action.

- By 2007, develop a system to collect data on pandemic influenza vaccine doses administered nationally and by State, age group, recipient (priority) group, and dose (1st or 2nd), and pilot test it in 10–15 States.
- The reporting system will use the HHS/CDC Countermeasures and Response Administration (CRA) Web-based, PHIN-certified system. Because national and State or local data and analysis needs and IT capabilities vary greatly; a single, inclusive system is not likely.
- Some States may want to use a system developed by HHS/CDC; others want a standard data set expectation with a standardized data exchange format/protocol. States may consider additional data requirements to meet their own needs.
- By 2008, complete system development and disseminate to all States.

Step 3: Develop protocol for use of population-based surveys, such as HHS/CDC's Behavioral Risk Factor Surveillance System (BRFSS), to provide national- and State-level estimates and to complement the vaccine tracking system described above.

- Define variables to be collected in surveys, such as age, gender, priority group, dose of vaccine received, where and when vaccinated, and reasons for nonvaccination, and modify the BRFSS to enable it to be quickly modified to rapidly determine vaccine coverage in key populations in the event of a pandemic
- Pilot test survey in States where vaccine tracking system is tested, to assess comparability of data collections

Step 4: Help States with tracking system plans.

Step 5: Define vaccine safety monitoring approaches through consultation with State immunization program managers to designate state-level vaccination adverse event coordinators. All adverse event systems will be examined for their ability to perform under pandemic conditions, and HHS will create a plan for coordinating the systems:

- Work with States to ensure timely reporting of adverse events to Vaccine Adverse Event Reporting System (VAERS) and other systems, and timely investigation of rare adverse events and clusters of adverse events.
- VAERS and other systems enhancements: Activation of a VAERS Emergency Preparedness Module will allow for receipt and processing of an additional 40,000 reports over a 3-month period above the annual baseline of 15,000 reports. This will be accomplished via hiring and training of additional staff by the VAERS contractor in addition to expanding and enhancing VAERS data systems.
- Consult with State immunization program managers and state adverse event coordinators (where those exist).

Step 6: Define Vaccine Safety Rapid Cycle Analysis (RCA) Program role in pandemic influenza vaccine adverse event reporting:

- Expand the Vaccine Safety Datalink (VSD) role for pandemic influenza vaccine adverse event surveillance. Currently the VSD RCA assesses data from eight Health Maintenance Organizations (HMOs) weekly for rare adverse events following immunization.
- To adequately perform surveillance for rare neurological adverse events (such as Guillain-Barre Syndrome [GBS]), this system would need to be expanded to be able to accurately and rapidly assess the risk for these events following vaccination.

Step 7: Establish real-time clinical active surveillance for select neurological adverse events (e.g., GBS):

- Assess 50 cases of clinically significant neurological complications following influenza vaccination. This pilot model of influenza vaccine safety monitoring and response system for clinically significant neurological complications can serve as an effective model for future vaccine campaigns that may occur in response to public health emergencies.
- Daily screening or review of VAERS reports and timely targeted followup of selected reports will enhance completeness and accuracy of VAERS report data.

Step 8: Develop vaccine effectiveness assessments that include, at a minimum, laboratory-confirmed emergency department visits, hospitalizations, and deaths, though not all outcomes will be assessed through all mechanisms:

- Establish mechanisms/protocol for assessing effectiveness of a pandemic influenza vaccine in preventing hospitalization and death among children and adults in HHS/CDC's NVSN

- Establish mechanism/protocol for assessing the effectiveness of a pandemic influenza vaccine in preventing hospitalizations and deaths among children and adults in the EIP sites
- Establish mechanisms in the VSD sites for vaccine effectiveness assessments in all age groups

Vaccine Education and Training

U. Action (No HSC Action): HHS will develop and implement training exercises for pandemic preparedness.

Timeframe: Within 12 months.

Measures of performance: Establish training courses and conduct training exercises on different aspects of the vaccine process.

Step 1: Specific vaccine-related training needs for pandemic influenza include those that surround the large-scale administration of a licensed or unlicensed pandemic influenza vaccine. These training efforts include activities to implement (1) vaccination clinics (clinic flow setup, vaccine storage and preparation, security requirements, client tracking/data entry, vaccine accountability); (2) Emergency Use Authorization (EUA) contingencies for administering an unlicensed or unapproved vaccine during a declared emergency; and (3) vaccine adverse event reporting.

Step 2: Define role of exercises and drills for implementing vaccination clinics. As a part of the advice that is developed for States for pandemic influenza vaccine clinic planning, exercises will be identified as a part of overall planning efforts. Within the advice, HHS/CDC will develop drill recommendations that include the following target goals (e.g., setup times, throughputs) for use in pandemic influenza clinic exercises:

- Develop vaccine adverse event reporting training materials
- Consult with public and private sector partners
- HHS/CDC will work with other Federal agencies, State immunization program coordinators, and private sector partners to establish target goals for pandemic influenza vaccination efforts and measurement indicators to assess those goals for overall preparedness assessment

Step 3: Develop materials and conduct training in a variety of formats:

- Clinic guideline development and general distribution
- Satellite broadcasts

- HHS/CDC Web site posting
- Web casts

Risk Communications and Public Information Campaigns

V. Action (HSC 6.1.12.1): HHS will collaborate with health care providers, industry partners, and State, local and tribal public health authorities to develop public information campaigns and other mechanisms to stimulate increased seasonal influenza vaccination. (Also see chapter 7, Pillar One, Action O [HSC 6.1.12.1].)

Timeframe: Within 12 months.

Measure of Performance: Domestic vaccine use increased relative to historical norms.

Step 1: Determine national influenza vaccination goals for seasonal use.

Step 2: Review capabilities needed for implementation.

Step 3: Define vaccination messages regarding rationale for priority groups, timing of vaccination, need for two doses, sites for vaccination, and importance of vaccination.

Step 4: Develop draft Vaccine Information Statements.

Pillar Two: Surveillance and Detection

Vaccine countermeasures are primarily a function of the preparedness and response components of this Plan. The results of surveillance and detection serve as a trigger for deployment of pre-pandemic and pandemic vaccine.

Pillar Three: Response and Containment

In the event of a pandemic, the expedient and seamless production of pandemic vaccine from generation and testing of influenza virus reference strains, to vaccine-manufacturing and lot-release testing, to vaccine packaging and shipment are key elements in the overall domestic pandemic response. Pillar Three actions deal with HHS facilitation of the provision of pre-pandemic and pandemic vaccines, when they become available, as part of a comprehensive response and containment effort against pandemic influenza. The transitions from the identification of clinical isolates to the ultimate shipment of finished vaccines from the vaccine distributions centers and then to the States are covered under Pillar Three. More comprehensive information for regulatory advice is provided in Appendix A—Vaccine Regulatory Guidelines.

Pillar Three actions on response and containment activities involve pandemic vaccine distribution during a pandemic (HSC 6.1.14 and 6.3.5), advice on vaccination practices (HSC 6.1.11), and the tracking of vaccine-related adverse events (HSC 6.1.13).

Leveraging National Medical and Public Health Surge Capacity

A. Action (HSC 6.3.5.3): HHS, in coordination with DHS, will allocate and assure the effective and secure distribution of public stocks of antiviral drugs and vaccines when they become available. HHS and DHS are currently prepared to distribute stockpile as soon as countermeasures become available.

Timeframe: As required and dependent on availability.

Measure of Performance: Number of doses of vaccine and treatment courses of antiviral medications distributed.

Step 1: Implement plan to monitor vaccine distribution.

Step 2: Collect data on monitoring vaccine distribution.

Step 3: Revise distribution plans of medical countermeasures according to pandemic severity, outbreak sites, countermeasure availability, and data gathered on virus behavior and pathogenic characteristics.

B. Action (no HSC action): HHS provides a roadmap for obtaining the needed information for the efficient submission of high quality Investigational New Drug applications (INDs), Emergency Use Authorization (EUAs), and Biologics License Applications (BLAs) for pandemic influenza vaccines.

Timeframe: Within 6 months.

Measure of Performance: Development of web-based interface reflecting this roadmap for vaccine manufacturers and other HHS agencies.

Step 1: Initiate development (pre-IND meetings and IND submissions).

Step 2: License vaccine, including accelerated approval (Draft Guidance for Industry, Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines, http://www.fda.gov/cber/gdlns/panfluvac.pdf).

Step 3: Fast track designation (Guidance for Industry, Fast Track Drug Development Programs—Designation, Development, and application review http://www.fda.gov/cber/gdlns/fsttrk.pdf).

Step 4: Obtain FDA advice on chemistry, manufacturing, and controls (CMC) and manufacturing facilities through meetings and other resources (Guidance for

Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product http://www.fda.gov/cber/gdlns/cmcvacc.pdf).

Step 5: Obtain FDA advice on EUA (Draft Guidance on Emergency Use Authorization of Medical Products http://www.fda.gov/oc/bioterrorism/emergency_use.html).

C. Action (HSC 6.1.13.10): HHS, with other federal departments, will work with DOJ to develop a joint strategic plan to ensure international shipments of counterfeit vaccine and antiviral medications are detected at our borders and that domestic counterfeit drug production and distribution is thwarted through aggressive enforcement efforts. (Also see chapter 1 Pillar One, Action V [HSC 6.1.13.10]; and chapter 6, Pillar Three, Action E [HSC 6.1.13.10].)

Timeframe: Within 3 months.

Measure of Performance: Joint strategic plan developed; international and domestic counterfeit drug shipments prevented or interdicted.

Step 1: Investigate reports of counterfeit drugs used for pandemic treatment or prophylactic purposes and prosecute cases as evidence warrants.

Step 2: Investigate reports of counterfeit vaccines used, and prosecute cases as evidence warrants.

Step 3: Use authorities and prescribed plans to remedy the illegal distribution of medical countermeasures.

D. Action (No HSC Action): HHS will select a pandemic virus isolate for virus reference strain production, construct, qualify, and ship pandemic virus reference strain to vaccine manufacturers.

Timeframe: Within 6 weeks of pandemic declaration.

Measure of Performance: Test exercise to determine operational status.

Step 1: Perform antigenic and genetic analyses to aid in the selection of appropriate pandemic virus reference strain(s).

Step 2: Conduct reverse genetic procedures:

- Good Laboratory Practice (GLP) protocols and standard operating procedures will be followed.

- Laboratory studies will be performed under enhanced Bio-Safety Level 3 (BSL3) conditions and facilities by personnel wearing protective equipment including Powered Air Purifying Respirators (PAPRs).
- Vero cells from a vaccine-qualified master cell bank should be used to recover viruses by plasmid transfection.
- The antigenic properties of the reference virus should be assessed and shown to be identical to that of the wild type virus from which the haemagglutinin (HA) and the neuraminidase (NA) segments were obtained.
- The nucleotide sequence of the HA and NA genes of the reference virus should be determined and should be compared with the sequence of the respective clones and of the genes from the original wild-type virus. Any differences should be noted. An assessment of the level of residual plasmid in the reference virus should be made using PCR technology.
- The virus titer should be determined in the appropriate substrate (eggs or Madin-Darby Canine Kidney cells).
- Absence of bacterial and/or fungal contamination will be established by culturing.

Step 3: Conduct safety testing of resulting vaccine reference viruses.

Step 4: Request USDA exemption of the reference virus from the Select Agent List by providing the following information:

- Data regarding the source of the viruses and genes; complete nucleotide sequence of the HA
- Pathogenicity testing results in chickens, per OIE standards
- Trypsin dependence of plaque formation by the reassortant in chicken embryo fibroblasts cell mono-layers

Step 5: Transfer of vaccine reference virus via USDA transport permit to vaccine manufacturers.

E. Action (No HSC Action): HHS will provide pandemic vaccine to store and distribute pandemic vaccines. (Also see Pillar One, Action O [HSC 6.1.13.5] above.)

Timeframe: Within 6 months.

Measure of Performance: Creation of the plan and training exercise of plan.

Step 1: Contract storage and stability testing of pandemic vaccine as needed at vaccine manufacturers and other designated sites.

Step 2: Contract distribution of pandemic vaccine with private sector distributors and other carriers.

Step 3: Institute prescribed physical security measures for vaccine manufacturing, distribution centers, critical suppliers, and transportation routes using pandemic plan and multilevel law enforcement team.

F. Action (No HSC Action): HHS will develop a plan to coordinate delivery of pandemic vaccine to designated sites within 12 months upon consultation with NVPO/HHS, OPHEP/HHS, State, local, and tribal public health departments. (Also see Pillar One, Action P [HSC 6.1.13.1,] and Pillar Three, Action A [HSC 6.3.5.3] above.)

Timeframe: Within 12 months.

Measure of Performance: Issuance of a vaccine delivery plan.

Step 1: Review and revise vaccination clinic guidelines using those developed in 2004 during the influenza vaccine shortage:

http://www.cdc.gov/flu/professionals/vaccination/pdf/vaxclinicplanning0405.pdf.

- Consult with public and private sector health leaders.
- Although the Public Health Service Act authorizes HHS to provide vaccines to States, it does not authorize HHS to provide vaccines directly to private entities. The Department would need new statutory authority to do the latter.

Step 2: Finalize pandemic vaccine delivery plan.

Step 3: Provide training for vaccine delivery through exercises.

G. Action (HSC 6.1.14.4): HHS, in coordination with DHS and Sector-specific agencies, DOS, DOD, DOL, VA, and Treasury, will present recommendations on target groups for vaccine and anti-viral drugs when sustained and sufficient human-to-human transmission of a potential pandemic influenza strain is documented anywhere in the world. The recommendations will reflect data from the pandemic and available supplies of medical countermeasures. (Also see chapter 6, Pillar Three, Action B [HSC 6.1.14.4].)

Timeframe: Within 2–3 weeks of outbreak.

Measure of Performance: Provisional identification of priority groups for various pandemic scenarios.

Step 1: Assist in the assessment of global needs and available resources globally and domestically.

Step 2: Provide recommendations on plans to assist and allocate available domestic resources.

H. Action (No HSC Action): HHS will review, revise, and implement tracking plan to monitor pandemic vaccination in consultation with vaccine manufacturers, vaccine distributors, and State immunization program managers. (Also see Pillar One, Action T [HSC 6.1.13.9] above; and chapter 2, Pillar Three, Action D [HSC 6.1.13.9].)

Timeframe: 12 months.

Measure of Performance: Completion of the vaccination monitoring plan.

Step 1: Implement vaccine effectiveness assessments among NVSN/EIP/VSD sites or other settings as feasible, depending on timing and spread of pandemic influenza and vaccine availability.

Step 2: Implement survey periodically (e.g., at least monthly) for reporting results in HHS/CDC's Epi-X and Morbidity/Mortality Weekly Report. The survey may be an expansion of the existing BRFSS or a separate focused survey using BRFSS infrastructure. In addition, use of followup surveys in which particular groups of respondents are identified during the BRFSS survey and followed up with a more extensive set of health surveillance questions at a later date is a potentially efficient means of expanding the utility of the current system.

I. Action (No HSC Action): HHS will develop plans for communications of vaccines and their usages, priorities, and limitations. (Also see Pillar One, Action Q [HSC 6.1.14.1] above.)

Timeframe: Within 6 months.

Measure of Performance: Issuance of vaccine communication plan.

Step 1: Develop a communications plan on pre-pandemic and pandemic vaccine production and vaccine's allocation, distribution, and usage.

Step 2: Review and revise vaccination messages regarding rationale for priority groups, timing of vaccination, need for two doses, sites for vaccination, and importance of vaccination.

Step 3: Develop Vaccine Information Statements.

Appendix 5–A: Vaccine Regulatory Guidelines

Vaccine regulatory issues: investigational new drug usage, emergency use authorization, and licensure. Particular regulatory approaches utilized depend on whether a pandemic were to occur now, next year, or several years from now. Approaches would reflect the availability of approved and investigational vaccines and the characteristics of circulating and emerging viruses. For all of the mechanisms of expedited/facilitated development or access, early and frequent interactions between the vaccine manufacturer/sponsor (government or commercial) and FDA are of the highest importance.

Emergency Use Authority

- During an emergency declared by the HHS Secretary, FDA may authorize the use of an unapproved vaccine or an unapproved use of an approved vaccine if certain legal requirements are met.
- If a declared emergency occurs before a vaccine development process is completed and alternatives are lacking, and in particular, if the vaccine appears sufficiently promising that the SNS might consider acquiring it for investigational use, then appropriate Government agencies and sponsors should focus on ensuring that complete data are rapidly provided to FDA to support issuance of an EUA.
- Data can be provided through pre-IND or IND submissions and discussion of ongoing and future development plans, as far in advance of need as possible.
- FDA would then assess whether the data would potentially support an EUA and provide advice on any additional studies and data that may be desirable both for further development and to support emergency use as warranted.
- Analysis of whether the available data and information support issuing an EUA if requested for temporary use in a declared emergency, and the timeframe in which this could be done, may depend on multiple factors such as the adequacy of data provided in advance, including the evidence for safety and immunogenicity/efficacy and the nature of the emergency.
- Therefore, advance submission and discussion of information from completed studies and plans for additional studies will be critical to minimizing the time required for additional evaluation after onset of an emergency, but the final determination regarding whether the criteria for issuance of an EUA are met can only be made after an emergency is declared.
- The Secretary of HHS may declare an emergency, justifying an EUA if he determines that a public health emergency exists that affects or has the significant potential to affect national security.

- The FDA Commissioner may issue an EUA if, after consulting with the Directors of NIH and CDC (to the extent feasible and appropriate), he concludes that it is reasonable to believe that the product may be effective; the known and potential benefits outweigh the known and potential risks of using the product; and there is no adequate, approved, and available alternative.
- FDA shall, to the extent practicable given the circumstances of the emergency, impose certain conditions on an EUA for an unapproved product and an EUA for an unapproved use of an approved product, and may impose certain other conditions.

Biologics License Application (BLA) Licensure Issues

- Currently there are no U.S. licensed influenza vaccines approved for pandemic avian influenza strains. FDA has stated on numerous occasions, and as recently as the November 29–30, 2005, National Vaccine Advisory Committee meeting, that for licensed manufacturers of interpandemic vaccines, use of a pandemic strain—for example, H5—would not require a new BLA, and in the setting of an evolving pandemic threat or actual pandemic, would be evaluated in an expedited manner as a strain change prior approval supplement to an approved BLA.
- License supplement would require information on the manufacturing of the strain and limited clinical data—for example, immunogenicity and safety data. In an emergency situation, depending on the quality of the data, FDA's review would be completed in an expedited manner.
- If the pandemic were to occur prior to licensure of a vaccine against the pandemic strain, or at a time when an investigational vaccine has advanced to the stage of human clinical trials under IND, but sufficient data have not yet been accumulated to support licensure of a BLA, there are several potential mechanisms FDA can use to facilitate the rapid access to these products, depending on the amount and quality of data submitted to the FDA for review.
- Adjuvant, cell-culture-based, and other new technologies would be considered a new product and, thus, would require the submission of a new BLA by all manufacturers, regardless of whether they are currently licensed to manufacture an egg-based influenza vaccine.
- If adjuvants are shown to be useful in dose sparing and added to candidate pandemic vaccines, this would significantly change the manufacturing process and the product itself, requiring immunogenicity and safety data and submission of a new BLA.
- Under accelerated approval the BLA would require manufacturing, safety, and immunogenicity data, as well as post-licensure confirmatory clinical studies.

- A pandemic influenza vaccine would be designated for a priority review during the interpandemic period. The unlicensed product could also potentially be made available through an IND or EUA.
- New and non-U.S. licensed influenza vaccine manufacturers' submission of a BLA for licensure of a pandemic influenza vaccine, regardless of the technology, (e.g., egg-based, tissue culture-based, recombinant) is required now and in the future.
- Under accelerated approval, BLA requires manufacturing and facility data as well as safety and immunogenicity data and post-licensure confirmatory clinical studies. FDA would consider data from clinical studies and use under licensure (for safety) in other countries in support of U.S. licensure along with safety and immunogenicity data for accelerated approval, but the data must support safety and effectiveness of the vaccine.
- Some technologies may not be appropriate for accelerated approval (e.g., a peptide conjugate vaccine where there is not a marker for protection). In the event of a pandemic, the review time could be significantly shortened depending on the quality of the data. The unlicensed product could also be made available through an IND or EUA.

Appendix 5–B: Vaccine Virus Reference Strain Development, Production, and Qualification

Inactivated influenza vaccines are produced from seed virus that exploits the extraordinary growth efficiency in embryonated chicken eggs conferred by the A/Puerto Rico/8/1934 (PR8) internal genes. Reassortants with the PR8 internal genes and the HA and NA surface protein coding genes from the novel potentially pandemic strain will be generated in the laboratory following WHO-sanctioned protocols and Good Laboratory Practice, which streamline downstream adventitious agent testing. The virus reference stock will be transferred to vaccine manufacturers. Live, attenuated vaccines are produced similarly using plasmids encoding target HA and NA genes of pandemic virus and donor genes containing mutations for temperature-sensitive and attenuation phenotypes.

The reverse genetics procedures will be performed as described in the WHO documents entitled *WHO Guidance on Development of Influenza Vaccine Reference Viruses by Reverse Genetics* http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_6/en/index.html. The process of virus rescue by reverse genetics requires 21 days. Subsequent production of virus stock and titration requires 4 days.

The safety of the resulting vaccine reference viruses will be tested according to the established WHO guidelines as described in *Production of Pilot Lots of Inactivated Influenza Vaccines from Reassortants Derived from Avian Influenza Viruses: An Interim Biosafety Risk Assessment* http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_RMD_2003_5/en/. All work with highly pathogenic avian influenza virus and their derivatives is regulated by the USDA Select Agents Program. Because removal of the polybasic amino acids from HA and re-assortment with PR8 results in loss of virulence and transmissibility in poultry, the USDA Select Agent Program is willing to review experimental evidence to this effect for each reference strain and remove it from the list if deemed safe. The reassortants that were excluded from the Select Agent regulations by USDA and meet the safety criteria of the 2003 WHO document will be made available to vaccine manufacturers for production of pilot lots of vaccine for experimental use and clinical studies.