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CHAPTER 6: ANTIVIRAL DRUGS

Introduction

FDA-approved antiviral drugs with activity against influenza viruses ("antivirals") include the M2-inhibitors adamantanes (*amantadine* and *rimantadine)* and the neuraminidase inhibitors (*oseltamivir phosphate* [Tamiflu®] and *zanamivir* [Relenza®]). Appropriate use of these agents during an influenza pandemic may reduce morbidity and mortality, and may diminish the overwhelming demands that will be placed on the health care system. Antivirals might also be used during the U.S. Response Stages 0, 1, and 2 for limited attempts to contain small disease clusters and potentially slow the spread of novel influenza viruses. A huge and uncoordinated demand for antiviral drugs early in a pandemic could rapidly deplete local and national supplies. It could also facilitate the emergence of antimicrobial resistance. Preparedness planning for the optimal use of antiviral stocks is therefore essential.

This chapter focuses on one specific pharmacologic countermeasure—antivirals—rather than a broad range of potential interventions for pandemic influenza. It discusses all aspects of the development, allocation, use, and monitoring of antiviral drugs. Therefore, the chapter is organized slightly differently from the other chapters and includes activities arranged chronologically from product concept and development, to the monitoring for efficacy and side effects of antiviral drugs administered for prophylaxis and treatment.

Antiviral drug focus areas relative to pandemic planning and response include the following:

- The detection of antiviral resistance in pre-pandemic and pandemic influenza viruses
- The applicability and linkage of influenza antiviral drug development and clinical evaluation for a pandemic situation, and maintenance of pre-pandemic drug stockpiles
- The global and domestic manufacturing capacity of antiviral drugs used for prevention and/or treatment of pre-pandemic and pandemic influenza virus infections
- The regulatory review processes for, and approval of, new antiviral drugs during pre-pandemic and pandemic periods
- The procurement, staging, and positioning of antiviral drug stockpiles during pre-pandemic and pandemic periods
- The prioritization and allocation strategies of antiviral drug usage during the pre-pandemic and pandemic periods

- The mechanisms for distribution of antiviral drug stockpiles during pre-pandemic and pandemic periods
- The evaluation of the efficacy of antiviral drugs against a pandemic strain as well as any associated adverse side effects
- The communication of antiviral drug policies and implementation actions
- The use of antivirals as part of an overall pandemic containment strategy

The actions covered by this operational plan on antiviral drugs include preparations prior to, at the onset of, and during an influenza pandemic.

Role of HHS in Antiviral Drugs

HHS' role with respect to antiviral drugs is to facilitate the development and use of these countermeasures during a pandemic. Specifically, HHS will:

- Establish and maintain antiviral stockpiles
- Support research projects to optimize dosing strategies for existing antiviral medications, identify novel drug targets, and develop compounds that inhibit viral entry, replication, and maturation
- Develop guidelines to assist State and local governments and other partners and stakeholders in defining groups that should have priority access to antivirals
- Monitor activities involved in the production and distribution of counterfeit antiviral drugs

Specific Assumptions and Planning Considerations for Antiviral Drugs

- The preparedness and response goal is to provide influenza antiviral drugs for at least 25 percent of the U.S. population.
- During the pre-pandemic period, HHS stockpiles of oseltamivir phosphate and zanamivir will be needed to reach a total of at least 81 million treatment courses for use in pandemic treatment by the States. The maintenance of a stockpile of adamantane class drugs will also be needed in the event a pandemic influenza virus is shown to be sensitive to this class of drugs.
- HHS will subsidize the purchase by the States of up to 31 (of the 81) million treatment courses of oseltamivir phosphate and zanamivir on a *pro rata* basis. The Federal direct purchase and Federal-subsidized purchases by the States of influenza antiviral drugs for pandemic purposes will provide coverage for 25 percent of the U.S. population, as recommended by WHO.
- At the beginning of a pandemic in the United States, the initial HHS strategy will be to delay the spread of pandemic via the rapid deployment of an additional 6 million treatment courses from the SNS for treatment and prophylaxis of contacts of confirmed cases in specific community outbreaks.
- As the pandemic progresses, antiviral drugs will be distributed *pro rata* to States primarily for medical treatment of infected persons presenting with disease symptoms.

HHS Actions and Expectations

Pillar One: Preparedness and Communication

Preparedness and communication as related to antiviral drugs include activities such as supporting novel research (including clinical trials) for new drugs, increasing capacity for manufacturing, facilitating antiviral drug approval, determining product assets for stockpiling, considering expansion of the Shelf Life Extension Program (SLEP), and developing Federal communications statements on antiviral use policies and recommendations for usage.

HHS actions in this chapter are intended to integrate the HSC actions and expectations concerning antiviral use during an influenza pandemic into a comprehensive domestic and global antiviral effort to include antiviral use coordination (HSC 4.1.6), planning (HSC 6.1.1), communications (HSC 6.1.3), stockpiling (HSC 6.1.5, 6.1.6, 6.1.7, 6.1.9), distribution mechanisms and allocations (HSC 6.1.13, 6.1.14), and novel strategies for development (HSC 6.1.17).

Antiviral Drug Development

A. Action (HSC 6.1.17.2): HHS shall collaborate with the pharmaceutical, medical device, and diagnostics industries to accelerate development, evaluation (including the evaluation of dose-sparing strategies), approval, and U.S.-based production of new antiviral drugs and diagnostics. Development activities should include design of preclinical and clinical studies to collect safety and efficacy information across multiple strains and seasons of circulating influenza illness, and advance design of protocols to obtain additional updated information to support revisions in product usage during circulation of novel strains and evolution of pandemic spread. Such collaborations should involve early and frequent discussions with the FDA to explore the use of accelerated regulatory pathways towards product approval. Collaborations concerning diagnostic tests should include CDC to facilitate access to pandemic virus samples for validation testing and ensure that the test is one that can be used to promote and protect the public health during an influenza pandemic. (Also see chapter 2, Pillar One, Action F [HSC 6.1.17.2].)

Timeframe: Within 6 months.

Measure of Performance: Initiation of clinical trials of new influenza antiviral drugs and diagnostics.

Step 1: Contract with manufacturers and research laboratories to support discovery, development, and preclinical and clinical evaluation of new antiviral drugs and new formulations of currently approved products; including the development of new formulations for special populations, such as infants and young children or elderly patients who cannot swallow solid oral dosage forms.

Step 2: Support clinical evaluation through the development of a clinical trial infrastructure on diagnostics, therapeutics, and natural history of avian influenza and other emerging infectious diseases.

Step 3: Contract with manufacturers and research laboratories to evaluate toxicology, pharmacokinetics, (including human challenge studies with a seasonal influenza strain), and effect of agents with antiviral potential in animal models; and, where appropriate, include potential for sublicensure from manufacturers of approved drugs.

Step 4: Ensure that results from Government-supported trials are expeditiously shared with Federal partners and submitted for publication, if appropriate.

Step 5: Evaluate initial components and activities that can be performed in the initial timeframe and ensure ongoing commitment to support and followup.

B. Action (No HSC Action): HHS will facilitate the expansion of domestic antiviral drug manufacturing capacity within 12 months.

Timeframe: Within 12 months.

Measure of Performance: The award of contracts for advanced development and U.S.-based production of new antiviral drugs and the encouragement of U.S.-based production of currently approved products acquired for the Strategic National Stockpile to expand the domestic antiviral drug manufacturers' capacity in the U.S.

Step 1: Engage current manufacturers of antiviral agents to expand domestic production.

Step 2: Award contracts for the advanced development toward U.S. approval and production of new antiviral medications.

Step 3: Identify mechanisms, including potential for sublicensure from manufacturers of approved drugs, if needed, to permit other manufacturers to produce proprietary antiviral agents.

C. Action (No HSC Action): HHS will conduct and provide advice for, respectively, clinical studies to evaluate the safety and efficacy of new antiviral agents or new formulations of existing agents to accelerate approval.

Timeframe: Within 6 months.

Measure of Performance: Publication of regulatory guidance and the initiation of collaborative clinical trials for evaluation of new influenza antiviral drugs.

Step 1: Enhance and expand collaborations with biotech and pharmaceutical companies for clinical evaluation of existing and new antiviral drugs.

Step 2: Enhance communication between FDA regulators and biotech and pharmaceutical companies evaluating existing and new antiviral drugs.

Step 3: Develop clinical protocols to test antiviral agents for safety and efficacy during the interpandemic period.

Step 4: Conduct clinical studies to assess prophylactic and therapeutic uses.

Step 5: Evaluate initial components and activities that can be performed in the initial timeframe and ensure ongoing commitment to support and followup.

Step 6: Encourage the development of new formulations for special populations, such as infants and young children, or elderly patients who cannot swallow solid oral dosage forms.

D. Action (HSC 6.1.15.3): HHS shall develop protocols and procedures to ensure timely reporting to federal agencies and submission for publication of data from HHS-supported influenza vaccine, antiviral medication, and diagnostic evaluation studies. (Also see chapter 2, Pillar One, Action D [HSC 6.1.15.3] regarding surveillance; and chapter 5, Pillar One, Action E [HSC 6.1.15.3].)

Timeframe: Within 6 months.

Measure of Performance: Study data shared with federal agencies within 1 month of analyses and publication of clinical trial data following completion of studies.

Step 1: Prepare procedures and plans to select and secure appropriate materials.

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

E. 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 the diagnostics, therapeutics, and natural history of avian influenza and other human emerging infectious diseases. 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, [HSC 4.1.6.2]; and chapter 5, Pillar One, Action C [HSC 4.1.6.2].)

Timeframe: Within 18 months.

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

Within the framework of supporting pharmacokinetic, animal model, and clinical studies to evaluate optimal dosing, treatment duration, and combinations of licensed antiviral medications for H5N1 and other potential pandemic strains, HHS will:

Step 1: Solicit proposals and support contracts for pharmacokinetic, animal, and clinical studies of optimal use of existing antiviral drugs for H5N1 and other potential pandemic strains.

Step 2: Award contracts to provide pharmacokinetic data and establish animal models and conduct clinical studies to evaluate antiviral drugs.

Step 3: Facilitate evaluation of current antiviral medications as treatment and prophylaxis for H5N1 and circulating influenza using a new clinical trials infrastructure with collaborative study sites in Asia.

Antiviral Drug Production, Stockpiling, and Storage

F. Action (HSC 6.1.6.1): HHS, with VA and DOD, will define quantities of specific U.S.-approved antiviral medications to include in national and state stockpiles consistent with the national pandemic response strategy, and develop and disseminate guidelines for their use during pre-pandemic and pandemic periods. (Also see chapter 4, Pillar One, Action D [HSC 6.1.6.2].)

Timeframe: Within 6 months.

Measure of Performance: Development of policy concerning selection, relative proportions, and use of antivirals in SNS and State stockpiles.

G. Action (HSC 6.1.13.2): HHS, in coordination with DOD, VA, States, and other public sector entities with antiviral stockpiles, will coordinate use of assets maintained by different organizations. (Also see chapter 8, Pillar One, Action Y [HSC 6.1.13.2].)

Timeframe: Within 12 months.

Measure of Performance: Plans developed for coordinated use of antiviral stockpiles.

H. Action (HSC 6.1.9.1): HHS will, to the extent feasible, work with antiviral drug manufacturers and large distributors to develop agreements supporting Federal procurement of available stocks of antiviral drugs during pre-pandemic and pandemic periods.

Timeframe: Within 12 months.

Measure of Performance: New antivirals procured by SNS within the constraints of industry capacity; Federal contracts in place with antiviral drug manufacturers and distributors.

I. Action (HSC 6.1.9.2): HHS, in collaboration with the States, will purchase sufficient quantities of antivirals to treat 25% of the U.S. population with reserve of 6 million treatment courses for outbreak containment.

Timeframe: Within 18 months.

Measure of Performance: 50 million treatment courses of antiviral drugs procured by SNS: States and tribes make stockpile purchases toward aggregate 31 million treatment course goal.

J. Action (HSC 6.1.7.3): HHS in collaboration with State/local partners shall procure and allocate sufficient stockpiles of countermeasures to ensure continuity of critical medical and emergency response operations.

Timeframe: Within 18 months.

Measure of Performance: Sufficient quantities of antiviral medications and other countermeasures procured and distributed between SNS and State stockpiles.

K. Action (HSC 6.1.5.1): HHS will encourage and subsidize the development of State, territorial, and tribal antiviral stockpiles to support response activities. (Also see chapter 8, Pillar One, Action U [HSC 6.1.5.1].)

Timeframe: Within 18 months.

Measure of Performance: State, territorial and tribal stockpiles of antiviral medication established and antiviral medical purchases made toward goal of aggregate 31 million treatment courses.

The following steps will be undertaken to address Actions F–K:

Step 1: Develop overall policy for national strategy with Federal partners and State, local, and tribal stakeholders consistent with the national strategy to acquire sufficient antiviral medications to treat 25 percent of the U.S. population and to contain initial U.S. pandemic outbreaks, establish an interagency working group to develop specific policies and recommendations for antiviral medications to include in national and state stockpiles.

Step 2: Develop integrated procurement plan for antiviral stockpiles consistent with interagency guidelines and manufacturers' capabilities.

Step 3: Disseminate advice for State antiviral stockpile purchases including information on Federal cost sharing.

Step 4: Negotiate and complete purchase contracts with manufacturers including ability for Federal and State purchases to be made under the Federal contracts.

L. Action (HSC 6.1.6.4): HHS, in coordination with DOD, VA and the States will maintain antiviral and vaccine stockpiles in a manner consistent with the requirements of FDA/DOD SLEP and explore the possibility of broadening SLEP

to include equivalently maintained State stockpiles. (Also see chapter 8, Pillar One, Action V [HSC 6.1.6.4].)

Timeframe: Within 6 months.

Measure of Performance: Compliance with SLEP requirements documented; decision made on broadening SLEP to State stockpiles.

Step 1: Include all currently approved antiviral drugs that are maintained in the SNS in SLEP. As needed, work with manufacturers to change the label to facilitate SLEP compliance.

Step 2: In collaboration with State and local health authorities, determine whether to extend SLEP to State and local stockpiles.

Step 3: If SLEP is extended to State and local stockpiles, develop and disseminate advice for compliance with SLEP requirements.

Antiviral Prioritization and Distribution

M. Action (HSC 6.1.14.1): HHS in coordination with DHS and Sector-Specific Agencies, as well as DOS, DOD, DOJ, DOL, VA, Treasury, and State/local governments, develop objectives for the use of and strategy for allocating vaccine and antiviral drug stockpiles during pre-pandemic and pandemic periods under varying conditions of countermeasure supply and pandemic severity.

Timeframe: Within 3 months.

Measure of Performance: Clearly articulated statement for objectives of use of medical countermeasure under varying conditions of supply and pandemic severity.

N. Action (HSC 6.1.14.2): HHS, in coordination with DHS and Sector-Specific Agencies, DOS, DOD, DOL, VA, Treasury, and State/local governments, shall identify lists of personnel and high-risk groups who should be considered for priority access to medical countermeasures, under various pandemic scenarios. (Also see chapter 5, Pillar One, Action R [HSC 6.1.14.2].)

Timeframe: Within 9 months.

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

The following steps will be undertaken to address Actions M and N:

Step 1: Establish an interagency working group to review clinical data, animal studies, and mathematical models relevant to potential antiviral drug strategies and impacts.

Step 2: Develop and disseminate advice on antiviral drug use objectives and strategies.

Step 3: Define potential priority groups for antiviral therapy in the event of limited or inadequate antiviral drug supply, including specific critical sectors and functions within sectors that need to be maintained.

Step 4: Collaborate with State and local health authorities and private sector partners to develop and disseminate advice for dispensing antiviral drugs consistent with objectives and strategies, including addressing potential legal barriers to dispensing strategies.

Step 5: Develop and disseminate advice on a strategy to rapidly review objectives, strategies, and target groups at the time of a pandemic and propose necessary changes.

O. Action (HSC 6.1.13.4): HHS, in coordination with DOD, VA, and in collaboration with State, local, and tribal governments and private sector partners, will assist in the development of distribution plans for medical countermeasures stockpiles to ensure that delivery and distribution algorithms have been planned for each locality for antiviral distribution. The goal is to distribute antiviral medications to infected patients within 48 hours of onset of symptoms. (Also see chapter 8, Pillar One, Action AA [HSC 6.1.13.4].)

Timeframe: Within 12 months.

Measure of Performance: Distribution plans developed.

Step 1: Determine the needs and available resources afforded by current Federal, State, local, and tribal plans for antiviral drug distribution.

Step 2: Develop a coordinated plan that meets overall Federal strategy.

Step 3: Remedy deficiencies in existing distribution plans to mesh with coordinated plans.

Step 4: Develop a unit of use packaging to improve efficiency of the initial dispensing operations.

P. 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. (Also see chapter 5 [Vaccines].)

Timeframe: As required and dependent on availability.

Measure of Performance: Number of doses of vaccine and treatment courses of antiviral medications distributed. HHS and DHS are currently prepared to distribute stockpiles as soon as countermeasures become available.

Step 1: Assess the security and availability of antiviral distribution plans for Federal and State stockpiles.

Step 2: Create or revise plans to remedy deficiencies including distribution network.

Antiviral Drug Training and Communication

Q. 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 ensure that States, localities, and tribal entities have developed and exercised pandemic influenza countermeasures distribution plans, and can enact security protocols if necessary, according to predetermined priorities. (Also see chapter 5, Pillar One, Action P [HSC 6.1.13.1]; and chapter 8, Pillar One, Action X [HSC 6.1.13.1]).

Timeframe: Within 12 months.

Measure 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 size, number, and location of storage facilities and develop plan for pre-pandemic storage and product stability testing.

- Consult with pharmaceutical manufacturing and distributors industry, State and local public health departments on the possible storage facilities and storage requirements.
- Develop agreements/contracts with relevant storage facilities to include appropriate physical security measures.

Step 2: Develop distribution guidelines for stockpiles of influenza antiviral drugs that may include standard commercial distribution contractors.

Step 3: Develop an integrated plan for physical security measures of domestic antiviral drug manufacturing facilities, distribution centers, stockpiles facilities, critical suppliers, and transportation routes by multi-level law enforcement team.

Step 4: Award contracts to private distributors to transport antiviral drugs to States prior to pandemic with built-in redundancy based on severe-case pandemic scenarios.

Step 5: Ensure compliance of storage facilities with Federal regulatory requirements for storage and monitoring of approved pharmaceutical products.

R. Action (HSC 6.1.3.1): HHS, in coordination with DHS, DOS, DOD, VA, and other Federal partners, will develop, test, and implement a Federal Government public health emergency communications plan (describing the government's strategy for responding to a pandemic, outlining U.S. international commitments and intentions, and reviewing containment measures that the government believes will be effective as well as those it regards as likely to be ineffective, excessively costly, or harmful). (Also see chapter 2, Pillar One, Action M [No HSC number].)

Timeframe: Within 6 months.

Measure of Performance: Containment strategy and emergency response materials completed and published on http://www.pandemicflu.gov; communications plan implemented.

Step 1: Review and revise antiviral drug prophylaxis and treatment messages regarding rationale for priority groups, timing of usage, definition of prophylaxis and treatment courses, sites for antiviral drug deployment, and importance and limitations of antiviral drugs.

Step 2: Develop Antiviral Drug Information Statements.

Pillar Two: Surveillance and Detection

Antiviral drug countermeasures are primarily a function of the preparedness and response components of this Plan. Surveillance and detection are critical to identify the onset of a pandemic and its introduction into the United States, as in each situation, antiviral drugs will be deployed as one tool of a containment response. Surveillance and epidemiological investigation will also provide data that will be critical to review and potentially revise antiviral drug use strategies.

Pillar Three: Response and Containment

HHS is responsible for containment activities using antiviral drugs including identifying (based on scientific data) priority groups to receive antiviral drugs, allocating and

delivering the antiviral drugs, communicating critical information, and monitoring the effects of the antiviral drugs in the population.

Pillar Three HHS actions listed in this chapter are intended to integrate the HSC actions and expectations concerning antiviral distribution from the SNS and other distribution centers to Federal, State, local, and tribal authorities (HSC 6.3.5).

A. Action (HSC 6.3.5.2): HHS, in collaboration with State, local and tribal governments, will develop and disseminate recommendations for the use, if any, of antiviral stockpiles for targeted post-exposure prophylaxis in civilian populations.

   Timeframe: Within 3 months.

   Measure of Performance: States, localities, and tribal entities have received recommendations for incorporation into response plans.

   Step 1: Allocate and distribute antiviral drugs from the SNS to support containment activities, if any, based on pre-pandemic planning.

   Step 2: Monitor antiviral drug distribution and dispensing.

B. 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 antiviral drugs when sustained and efficient human-to-human transmission of a potential pandemic influenza strain is documented anywhere in the world. These recommendations will reflect data from the pandemic and available supplies of medical countermeasures. (Also see chapter 5, Pillar Three, Pillar G [HSC 6.1.14.4].)

   Timeframe: Ongoing coordination.

   Measure of Performance: Provisional identification of priority groups for various pandemic scenarios through interagency process within 2–3 weeks of outbreak.

   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.

C. Action (HSC 6.1.13.9): HHS, in coordination with DOD, VA, and in collaboration with State, territorial, tribal, and local partners, will develop/refine mechanisms to: (1) track adverse events following antiviral administration: (2) define protocols for conducting antiviral-effectiveness studies during a

pandemic. (Also see chapter 2, Pillar Three, Actions C and D [No HSC numbers]; and chapter 5, Pillar One, Action T [HSC 6.1.13.9].)

Timeframe: Within 18 months.

Measure of Performance: Mechanism(s) to track antiviral medication coverage and adverse events developed; antiviral medication coverage and adverse events developed; antiviral-effectiveness study protocols developed.

Step 1: Analysis of pandemic surveillance data and implement/communicate prophylaxis and treatment priority guidelines based on epidemiology of pandemic disease on a monthly or as needed basis during a pandemic. Antiviral drug use strategies will be revised as needed, as the pandemic progresses, to include:

- Review the epidemiology of initial pandemic influenza outbreaks including any available data on the effectiveness of antiviral drug treatment and prophylaxis and antiviral resistance
- As needed, revise advice on antiviral drug use to optimize the pandemic response
- Coordinate rapid disseminated revised advice through public and private sector partners (e.g., ASTHO, NACCHO, CSTE, AIM, AMA, ACP, AAP, AAFP, American Nurses Association (ANA), and National Influenza Vaccine Summit)

Step 2: Coordinate with VA, DOD, and State and local health departments to monitor the dispensing and impacts of influenza antiviral drugs during a pandemic within 1 month of the onset of a pandemic in the United States; by publishing a plan for coordination identifying the roles and responsibilities of each entity for the successful tracking, reporting, and utilization of gathered results to inform revision of antiviral drug strategies during a pandemic; through:

- Tracking antiviral drugs deployment:
  - Track asset allocations to each State, territorial, or local health department
  - Provide advice to Federal Agencies to allot and track antivirals distributed by Federal medical care providers (e.g., VA, Indian Health Service [IHS], Bureau of Prisons)
  - Review and revise, as needed, antiviral drug allocation and distribution among States, local and tribal governments, and Federal health care providers
- Assessing antiviral drug coverage using preestablished tracking systems and special studies

- Assessing effectiveness of antiviral treatment and prophylaxis in clinical and epidemiological studies:
  - Analyses of antiviral effectiveness must take into account characteristics that vary among individuals and those that vary with the time course of a pandemic, including diagnostic practices, length of time to initiation of therapy, and changes in the pandemic virus itself.
  - Such studies can be conducted using the existing infrastructure of the Emerging Infections Program sites and the New Vaccine Surveillance Network sites, with the allocation of additional resources.
- Monitoring adverse events associated with the treatment or prophylactic use of antivirals:
  - Review of reports to FDA through MedWatch monitoring program.
  - Assist State and local health departments and hospital and health care providers by downloading MedWatch forms (available at http://www.fda.gov/medwatch/) for distribution to each person receiving an antiviral drug, either for treatment or prophylaxis.
  - Develop a State and local campaign to educate health care workers on the mechanisms for reporting adverse events via the MedWatch program. This campaign should also address the potential side effects associated with the use of antiviral drugs for influenza.
  - Work with FDA's Adverse Events Reporting System (AERS) on a regular basis.
  - Active monitoring for adverse events among patients presenting for care in a network of emergency departments, through the existing National Electronic Injury Surveillance System Cooperative Adverse Drug Event project (NEISS-CADE), maintained by CDC and FDA.
  - HMO Research Network Center for Education and Research in Therapeutics (CERT), an integrated pharmaco-epidemiology program of 7.7 million patients, can also be used to monitor for adverse events.
- Monitoring antiviral drug resistance to pandemic influenza viruses with State and local partners

D. Action (no HSC Action): HHS and State and local health departments communicate messages on antiviral drug use and effectiveness throughout the course of a pandemic within a reasonable time period. (Also see chapter 7, Communications.)

Timeframe: Within 12 months.

Measure of Performance: Publish a plan of communications demonstrating responsible reporting of antiviral drug news to the public.

Step 1: Define messages regarding rationale for priority groups and antiviral drug use objectives and strategies.

Step 2: Develop and disseminate other key messages as needed.

E. Action (HSC 6.1.13.10): HHS with DOJ, DHA, DOS, and DOC institute an expanded plan for investigation and prosecution of cases involving counterfeit influenza antiviral drugs during a pandemic within one (1) month. (Also see chapter 1, Pillar One, Action V [HSC 6.1.13.10]; and chapter 5, Pillar Three, Action C [HSC 6.1.13.10]).

Measure of Performance: Publish an expanded and updated plan of action to handle counterfeit drugs and file indictments for cases of these counterfeit drugs.

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

Step 2: Use authorities and prescribed plans to remedy the illegal distribution of medical countermeasures.

Step 3: Monitor illicit promotion and trade of fraudulent remedies and communicate findings.

Appendix 6–A: Antiviral Drugs: IND, EUA, and Approval

There are four antiviral drugs approved for treatment and/or prophylaxis of influenza A.

A pandemic virus is expected to be a strain of influenza A, and the approved indications do not distinguish between pandemic and nonpandemic strains. The effect of a drug against different strains of influenza A is assessed using a combination of clinical trial and microbiologic data.

There are several potential mechanisms for facilitating access to unapproved drugs and unapproved uses of approved drugs, depending on the amount and quality of data submitted to FDA for review. These mechanisms include certain types of protocols under an IND or EUA, and are described briefly below.

IND

- Submission of complete IND clinical protocol for FDA review.
- Sufficient preexisting preclinical and clinical data to support protocol.
- Complete description of manufacturing process and quality control testing procedures as well as complete testing results.
- Informed consent.
- IRB approval and possible local IRB approval at every site.
- Monitoring and reporting to FDA as per 21 CFR 312.
- May require onsite facilities inspection by FDA, especially for new manufacturers.
- Certain IND requirements can be waived pursuant to 21 CFR Part 312. Informed consent cannot be waived.

EUA

See draft guidance (cited below) for recommendations on preclinical and clinical data needed to support EUA. It is often advantageous, and may be important, to submit such data in advance via a pre-IND or an IND.

- The Secretary of HHS declares an emergency justifying the EUA.
- Based on the totality of scientific evidence available, it is reasonable to believe that (1) the product may be effective; (2) the known and potential benefits outweigh the known and potential risks, and (3) 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.

For Antiviral Drugs Already on Hand in Stockpile Used for Approved Indications

No additional approval actions are required. To facilitate increased production, companies should submit proposals and information on additional facilities they wish to qualify as far in advance as possible, usually as manufacturing supplements to existing New Drug Applications (NDAs). FDA would review these submissions and conduct needed inspections as expeditiously as possible. Time required for review and inspection may vary depending on factors such as the following:

- The nature of the product. (Some antivirals have very complex manufacturing processes.)
- Complexity of the submission.
- Location of facilities. (International inspections may take months to schedule and carry out for logistic and resource reasons.)
- Staffing.

To the extent possible, such expansions of capacity should be carried out through pre-pandemic planning. If acute shortages occur in an emergency situation, FDA will work with manufacturers to expedite additional qualification of facilities and review of importation proposals. Lead time required for manufacturing the principal influenza antivirals would limit any contribution of new facilities in emergency situations. The major limiting factors in the timeline for increasing supply would be the time required for manufacturers to identify and equip facilities, conduct enough initial manufacturing to demonstrate quality, and scale up the multiple complex steps required for the principal influenza antivirals.

For Antiviral Drugs on Hand in Stockpile Used for Unapproved Indications

If use of stockpile holdings for an unapproved use is warranted, this could occur through sponsorship of an IND, for example, by a Federal entity such as CDC, which would submit the IND to FDA for review. An EUA might be appropriate (as described below) for unapproved uses of approved drugs; however, most currently stockpiled influenza products probably would be used for labeled indications.

Potential Plans for Development of Unapproved New Drugs That Might Be Useful for Future Stockpiling

During the interpandemic period, Government entities supporting drug development (e.g., HHS/NIH) should determine their level of support for new drug discovery and development, and should ensure that the Government or commercial sponsors of

appropriate new drugs or new uses of existing drugs submit as much information as possible to FDA as early in the process as possible. New drugs would require evaluation for safety and efficacy for their intended use and dosing, in addition to assessment of manufacturing information. Time constraints in the development process include time needed for sponsors to prepare data to support IND and, eventually, NDA submissions, including factors such as the following:

- Performing animal toxicology studies in vitro (and in vivo as appropriate) activity studies to support initial use in humans
- Initial safety and pharmacokinetics studies in humans to support dosing for efficacy studies
- Studies of efficacy in human influenza illness
- Chemistry, manufacturing, and controls information to support quality of product

Each of the above steps may take months, or in some instances, even years. The time needed for development studies reinforces the importance of early contact with FDA for discussion and advice to facilitate efficient approaches to development.

Facilitating and Expediting Development

FDA will be prepared to review pre-IND, IND, and NDA submissions expeditiously when adequate information is submitted. Timeframes for the review process may vary depending on the nature of the product, the type and complexity of data available, and staffing. Several mechanisms for facilitating and expediting development and approval are available, including the following:

- Pre-IND consultations: Allow early interaction for advice on development issues before enough information is available to support an IND submission for initiation of clinical studies. Contact review division for instructions on submission and early interaction.
- Fast Track designation: Allows for enhanced frequency of meetings and other interactions between FDA and sponsors of new drug development; see Guidance for Industry, Fast Track Drug Development Programs—Designation, Development, and Application Review at http://www.fda.gov/cder/guidance/5645fnl.htm.
- Priority review: Shortens usual timeframe for review of a complete NDA after suitable clinical trials are completed under IND; see Priority Review Policy at http://www.fda.gov/cder/mapp/6020–3.pdf.
- Expedited review of manufacturing supplements (Requests for Expedited Review of NDA Chemistry Supplements http://www.fda.gov/cder/mapp/5310–3.pdf).
- Accelerated approval: 21 CFR 314 Subpart H (314.500–314.560), Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, may allow

approval based on surrogate endpoints expected to be reasonably predictive of clinical benefit.

Enhancing Access to Unapproved Drugs While Development Is Ongoing

In the event of a pandemic, there are several potential mechanisms for facilitating access to an unapproved drug or an unapproved use of an approved drug, depending on amount and quality of data submitted to FDA for review. These mechanisms include the following:

- Investigational clinical protocols under standard IND regulations.
- Single-patient emergency INDs are unlikely to be useful in a pandemic setting. (See 21 CFR 312.36, Emergency use of an investigational new drug.)
- Treatment INDs (21 CFR 312.34, Treatment use of an investigational new drug).
- Emergency Use Authorization. (See draft guidance at http://www.fda.gov/oc/bioterrorism/emergency_use.html.)

Under exceptional circumstances, if an NDA is well advanced in the review process, additional expediting of approval could be considered on a case-by-case basis. For all of these alternatives, note that unapproved drugs are not usually manufactured in sufficient quantities to have a large immediate impact on total drug supply in an emergency.

Timing of Interactions

For all of the mechanisms of expedited/facilitated development or access above, early interactions between the drug sponsor (Government or commercial) and FDA are of the highest importance. Pre-IND interactions are encouraged. Review of pre-INDs and INDs (for protocols to initiate human study of a new drug) is typically accomplished within several weeks (30 days for new INDs), and review of NDAs (for marketing approval/licensure after completion and submission of adequate and well-controlled human clinical trials providing substantial evidence of efficacy and safety) typically is accomplished within 6 months for priority review. Shorter times sometimes may be possible if provisions such as rolling submission are employed, if data are compelling and provided in accessible form, and if staffing is adequate. FDA recognizes the emergency issues and the need to balance expedited turnaround with due attention to safety and efficacy. In each case the review process may identify substantial issues in development requiring further study and generation of additional data by the sponsor. In general, the limiting factor for duration of drug development will be time required by the sponsor to perform studies and submit data for review. Accumulation of adequate safety and efficacy data for risk–benefit assessment will be crucial for drugs that may be administered to thousands or millions of people on short notice, many of whom may not have serious disease without the drug (e.g., if drug is used for prophylaxis or mild disease).

EUA

Appropriate Government Agencies and sponsors should focus on ensuring that complete data are provided to FDA. Complete data are especially important if at any time during the course of development it appears that an unapproved drug or an unapproved use of an approved drug might be suitable for use under an EUA—if a declared emergency occurs before its development process is complete and alternatives are lacking, and in particular if the drug appears sufficiently promising that the SNS might consider acquiring it for investigational use. 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 the ability of the data to potentially support an EUA, and provide advice on additional studies and data that may be desirable both for further development and to support emergency use as warranted. The amount of data and information needed to support an EUA will depend on the nature of the product and completed studies and the nature of the emergency. EUA use of a drug is limited to the duration of a declared emergency (and allows patients to finish treatment courses they started during an emergency), after which investigational product regulations would apply. 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, the nature of the emergency, and the adequacy and availability of approved alternatives. Therefore, advance submission and discussion of information from completed studies and proposals for additional studies will be critical to minimizing the time required for additional evaluation after onset of an emergency. The final determination whether the criteria for issuance of an EUA are met can only be made after an emergency is declared.

Effect of the Timing of a Pandemic

There could be some differences in use of various emergency approaches described above, depending on whether a pandemic occurs this year or several years from now. These would not necessarily involve changes in general regulatory principles but could reflect availability of drugs and characteristics of circulating and emerging viruses. Examples of such differences include the following:

- If substantially greater quantities of approved drugs are manufactured and added to the stockpile before a pandemic, there may be less need to consider expedited addition of production facilities or use of any unapproved drugs or unapproved uses of approved drugs under EUA.
- If influenza viruses accumulate mutations to display greater resistance to approved drugs while maintaining virulence and transmissibility, the usefulness of stockpiled drugs could diminish even if supply is large, and the need to consider use of investigational drugs under IND or EUA could be greater if any new drugs with potentially better activity are at suitable stages of development.

- If drug discovery and research study efforts lead to new drugs with favorable risk/benefit for influenza treatment and prevention, and if studies are completed that support approval of any such drugs, there would be less need for EUA consideration because of availability of a greater range of marketed drugs.
- If (although currently thought to be unlikely) a pandemic strain were to arise that would be susceptible to the older adamantine influenza drugs (to which the recent H5N1 human strains have developed resistance), supply of these drugs would considerably augment the currently limited supply of the newer neuraminidase inhibitor drugs, and could decrease the need to consider expedited addition of production facilities or use of any unapproved drugs or unapproved uses of approved drugs under an EUA.

None of these possible differences is a certainty: the most important factors in regulatory interactions would still be early planning to generate data to support use of appropriate drugs, and early contacts with FDA to submit data and discuss development plans.

Differences Between Data Required for New Antiviral Drugs and New Uses of Existing Drugs

- Although INDs and EUAs might be considered either for use of new antiviral drugs or for new uses of existing drugs in an emergency if suitable data are available, the amount of new information that would have to be generated to support such use would differ depending on prior experience with the product, as well as factors such as intended population (e.g., treatment of gravely ill patients without other treatment options vs. prophylaxis of low-risk persons likely to have good outcomes without treatment).
- If there is a product already approved for human use whose unapproved use would have utility in an influenza emergency, the existing approval reflects the existence of a sufficient safety database for administration to humans under the labeled indication, and the amount of additional safety information needed to support the use against influenza might not be large depending on the intended dosing and populations. In the current situation it is unlikely that unapproved uses of approved drugs would significantly contribute to drug availability in an emergency.
- For unapproved new drugs, the amount of additional information needed to support emergency use would vary depending on the stage of development and extent of previous studies. For example, if there have already been extensive human studies of the proposed dosing regimen with data submitted for Agency review before emergency circumstances arise, evaluation of the risks and benefits for emergency use may be much more rapid and require far less additional data generation than for a drug just starting development for which available safety data are minimal and the potential for adverse events with widespread use, as well as the potential for benefit, may be extremely uncertain.

Appendix 6–B: SNS Operations—Pandemic Influenza Response

1. ***Mission.*** To deliver critical medical assets to the site of a national emergency.

2. ***Execution.***

   a. Concept: There are two main types of commodities stored in the SNS for a pandemic flu outbreak: those that are in mass quantity and will be delivered pro rata to project areas, ideally before local pandemic disease occurs; and those that are limited in quantity that will be targeted as needed during the pandemic outbreak. Whereas antiviral drugs and masks/respirators are in the former category and will be deployed in two initial phases, other medical assets are in the latter category (limited quantities) and will be deployed in a third phase.

   Phase 1: The best antiviral drug distribution strategy would be a *pro rata* phased deployment pushing product proactively to a single location in each of the 62 project areas. Upon direction of the CDC director, SNS will push antiviral drugs to the State, local, territorial, and tribal (SLTT) project areas prior to receipt of a request. This will ensure that SLTTs receive supplies before the need for assets becomes critical. Antivirals will be the first asset to be delivered to SLTTs and will comprise Phase 1 of the pandemic SNS response, estimated to take about 7 days. There is also a need to distribute antiviral drugs to Federal Agencies that provide health care such as the VA and Indian Health Service, and possibly to other sites targeted to preserve Federal government continuity of operations. Planning for these deployments will occur as prioritization and allocation decisions are made.

   Phase 2: Masks and respirators are available at the SLTT level, but they will be used up quickly. SLTTs will have a minimum surge capacity for these supplies. Masks/respirators will be allocated *pro rata* and shipped immediately after antivirals to the 62 project areas as Phase 2 of the response. This second deployment of assets will take between 7 and 10 days (after Phase 1 is completed due to the logistical challenges associated with product configuration).

   Phase 3: The final phase would be shipping SNS high demand but scarce resource commodities such as ventilators, other personal protective equipment (PPE) (protective face shields, gowns, gloves), and IV antibiotics. This last phase requires more scrutiny and a case-by-case approval process as SLTTs make their requests. Because of the relatively low numbers, SNS will be able to ship these assets on an as-requested basis. All requests must be sent to the

CDC Director's Emergency Operations Center (DEOC) through the State Governor or Governor's designee similar to a traditional SNS response as laid out in *Version 10*; *A Guide for Preparedness—Receiving, Distributing, and Dispensing Strategic National Stockpile Assets.*

Pushing product to the SLTTs in the first two phases will allow the Federal Government to be proactive and anticipate SLTT needs, increasing the chance of a successful response. It will also allow SNS to maintain surge capacity with additional items and be able to ship them rapidly during a pandemic at the time of need. Shipping product out before a pandemic and before an SLTT requests such will also ensure that the SNS staff and Federal transportation partners are available in full capacity to aid in the Federal response, and ready to respond to other events. During a pandemic, there is a high likelihood that resources such as personnel and trucks will be in limited supply, possibly affecting SNS response time.

b. Coordinating Instructions:

- A significant amount of material will arrive in a very short period of time, placing a much greater logistical burden on SLTTs. Therefore:
  - SLTTs must be prepared for large scale SNS shipments by establishing robust local Receipt, Storage, Staging (RSS) sites (12,000 square feet).
  - SLTTs must plan for additional warehouse space for storage of large quantities of material for an indefinite period of time.