Guidance for Industry

Influenza: Developing Drugs for Treatment and/or Prophylaxis

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2009
Clinical Antimicrobial

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TABLE OF CONTENTS

Guidance for Industry[1] Influenza: Developing Drugs for Treatment and/or Prophylaxis

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment and/or prophylaxis of illness caused by influenza viruses A and B, including both seasonal and pandemic varieties.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and designs of clinical and nonclinical studies to support the development of influenza drug products.[3] This guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and the public.[4] As the science of influenza treatment and prophylaxis evolves, this guidance may be revised.

Sponsors considering development of antiviral drugs for the treatment or prophylaxis of disease with novel influenza strains, or in a pandemic influenza setting, are encouraged to consult this

[1] This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Influenza viruses are designated by type (A, B, or C), subtype (specifically for influenza A: H and N numbers based on 16 hemagglutinin and 9 neuraminidase antigens), and by strain within types or subtypes. During a typical annual influenza epidemic, influenza B and two principal subtypes of influenza A (H3N2 and H1N1) circulate in varying proportions. New strains arise by ongoing antigenic drift within each of these types or subtypes. Many other influenza A subtypes occur in other host species, principally birds, and may cause occasional sporadic human infections. Influenza C has been reported as a cause of only sporadic mild disease and has not been a focus of either drug or vaccine development to date.

[3] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[4] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of influenza drug products.

guidance and to communicate with the FDA through the pre-investigational new drug application (pre-IND) consultation program and frequently throughout drug development. Proposals for fast track designation can be considered at any time during development, depending on appropriate fulfillment of the designated criteria.

This guidance does not address drug development for the treatment and/or prophylaxis of influenza C. This guidance also does not address development of influenza vaccines or vaccine adjuvants. Inquiries regarding vaccines should be addressed to the Center for Biologics Evaluation and Research (CBER).

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[5] This guidance focuses on specific drug development and trial design issues that are unique to the study of influenza.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Effective vaccines are the central element in influenza control, but antiviral drugs are used for treatment of established influenza illness, and for postexposure or pre-exposure prophylaxis in selected situations. Antiviral drugs have been approved for treatment or prophylaxis of influenza A, influenza A and B, and influenza (not otherwise specified) based on studies in illness caused by circulating influenza virus strains. Approved antiviral drugs for influenza fall into two classes, adamantanes and neuraminidase inhibitors, with studies and approvals extending over several decades.

Recent concerns about the possibility of pandemic spread of novel influenza strains have increased interest in influenza drug development;[6] however, seasonal influenza is also a major public health concern. The close relationship between seasonal and pandemic influenza warrant considering them together in discussions of regulatory approaches.

Although terms such as *avian influenza*, *epidemic influenza*, and *pandemic influenza* have been used interchangeably in some scientific and media publications, they have important differences. Avian influenza refers to any of a number of subtypes and strains that might be transmitted from birds to humans causing sporadic cases and clusters, and that might subsequently acquire

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[6] See documents and information at http://www.pandemicflu.gov.

capacity for rapid and widespread human-to-human transmission. Epidemic influenza refers to a greater number of cases of influenza illness occurring in a community or region during a given period of time. Pandemic influenza refers to a strain of predominantly avian, mammalian, or reassortant origin that has acquired capacity for transmission among humans and has emerged as a novel cause of widespread disease, dominating or replacing previously circulating subtypes (seasonal influenza) in human populations. Although sporadic cases of novel strains raise concerns regarding potential pandemic strain emergence, composition of these strains cannot be predicted with confidence even at the subtype level. In addition, substantial additional genetic change is likely as a novel strain progresses from sporadic to pandemic. Once a pandemic strain has passed through the population, it is expected from historic example that the same subtype will continue to circulate for some years after the pandemic subsides. That subtype would then be considered as *seasonal* influenza, and at some point would be replaced (or dominated) by the next emergent pandemic variant.

III. DEVELOPMENT PROGRAM

A. General Considerations

Influenza drug efficacy is evaluated in clinical trials conducted in the setting of circulating, naturally occurring influenza illness; however, a drug effective in the treatment of seasonal influenza may not be effective or as effective in pandemic influenza. Thus, information on potential differences in drug responsiveness among strains or subtypes, including avian strains isolated from human infections, should be explored by generating additional data from cell culture and animal studies, as well as the collection of clinical data when feasible.

Because of the public health implications of both epidemic and pandemic influenza, the variable nature of the disease, and limited therapeutic options and challenges in studying new options, novel approaches to drug development are of great interest. Development pathways can be designed to provide information supporting access to investigational drugs if public health emergency circumstances arise during the development process. Another important consideration is advance development of protocols for further exploration and verification of drug effects under changing epidemic and pandemic conditions.

1. Nonclinical and Early Phase Clinical Development Considerations

Before initiating clinical trials, sponsors should investigate the mechanism of action and antiviral activity of the candidate drug using multiple types, subtypes, and strains of influenza virus derived from human clinical infections and from animals that could serve as sources for new clinical strains. For a candidate drug with a mechanism other than direct antiviral effect, sponsors should conduct cell culture, biochemical, and genetic studies to support their animal toxicity studies (e.g., mouse knockout of the proposed target, receptor binding studies, and amino acid sequence homology analyses). Different proposed mechanisms of action may affect the types of studies warranted to explore risk-benefit balance (e.g., potential effects of immunomodulators on disease processes in patients with pre-existing immunologic abnormalities).

Candidate drugs should be assessed for activity in cell culture assays and, on the basis of those results, for in vivo activity in appropriate animal models of influenza infection. Sponsors should assess effects of candidate drugs on other pathogens that mimic or complicate influenza, including other respiratory viruses and bacteria associated with similar illnesses or complications.

Animal studies can be used to:

- Explore a candidate drug's activity against various strains of influenza including novel strains
- Explore the effects of inoculum size
- Compare dosing regimens and routes of administration
- Determine concentrations of drug at appropriate anatomic sites
- Explore exposure-response relationships
- Explore activity in immunocompromised hosts
- Characterize viral resistance and transmissibility
- Characterize treatment timing relative to onset of evident illness

Proposals for animal studies should include supporting information on the selection and characterization of the model, and details of the natural history of disease in the model, as well as the proposed study design. When designing animal studies, sponsors should consider factors such as the relevance of the viral strain and need for adaptation to the host, the natural history of disease in the animal model, viral inoculum effects, drug/dose and timing effects, and available information linking to human exposure-response and outcomes.

Cell culture and animal model studies should not be considered a substitute for clinical trials, but they can make valuable contributions to clinical trial designs, including dosing considerations and resistance monitoring plans, and can assist in exploring the generalizability of clinical trial results.

Virologic assessment and resistance monitoring are integral to antiviral drug development for influenza. Sponsors should address virologic plans and proposals together with their proposals for nonclinical and clinical studies throughout the development process beginning with pre-IND interactions.

a. Phase 2A: Challenge studies

After initial activity assessments and phase 1 human pharmacokinetic (PK) and tolerability studies, several sponsors have performed challenge studies. In challenge studies, healthy volunteers are inoculated with established challenge strains of influenza virus and administered an investigational antiviral drug either before (prophylaxis studies) or after (treatment studies) inoculation with the challenge strain. Challenge strains are attenuated viruses that produce a much milder set of symptoms compared to naturally occurring influenza. Pharmacodynamic (PD) endpoints in challenge studies include measurements such as clinical respiratory symptoms, nasal discharge weight, and quantitative measurements of viral shedding in nasal washes.

Challenge studies can provide useful exposure-response and safety information and the opportunity to demonstrate pharmacological antiviral activity in humans under controlled conditions outside the influenza season. Data from challenge studies contribute to dose selection for phase 2B and phase 3 studies and provide the opportunity to explore the effects of different times of drug initiation relative to virus exposure. However, challenge studies should not be considered efficacy trials for purposes of marketing approval, because challenge strains are attenuated viruses that produce a much milder set of symptoms compared to naturally occurring influenza. In addition, challenge study results may not predict treatment outcomes for novel circulating influenza strains and pandemic strains because tissue distribution, viral replication, and host responses to novel strains could vary from those recognized in well-characterized challenge strains.

Challenge studies are dependent on the availability of adequately safety-tested challenge strains and consideration of the ethics of challenge studies. Proposals for challenge studies should include documentation of the safety testing and biologics investigational new drug (IND) status (in CBER) of the influenza challenge strains. Appropriate coordination and consultation with CBER staff reviewing the INDs for use of any new challenge strains is important; using novel strains of high or unknown pathogenicity is not an option for reasons of ethics, safety, and containment.

Sponsors should provide dosing rationale for challenge studies on the basis of animal and human PK and tolerability data, cell culture EC_{50} values, animal model PK/PD data, and any other relevant information.

b. Phase 2 dose-ranging studies

The design of phase 2 dose-ranging studies depends on the type of population intended for phase 3 studies, as well as the initial safety profile of the investigational drug. We strongly recommend that sponsors conduct phase 2 studies before designing phase 3 trials. Proceeding directly to phase 3 from phase 1 or phase 2A studies may fail to produce interpretable or useful phase 3 data, especially if selection of doses and regimens are not well founded. Phase 2 dose-ranging studies usually are designed with statistical power to look at differences in viral shedding (e.g., duration, quantitative differences from baseline). Differences in clinical symptoms are included as secondary endpoints. Differences in virologic endpoints together with numerical trends in clinical symptoms are used to choose doses for further study in phase 3.

It should be noted that clinical dose-response studies are one type of adequate and well-controlled study that, if measuring appropriate endpoints in appropriate populations, can contribute to substantial evidence of effectiveness (21 CFR 314.26). In addition, exposure-response studies and analyses within studies can provide support for approval of different doses, dosing regimens, or dosage forms. Depending on the study endpoints, exposure-response information can:

- Help to connect in vitro antiviral activity (EC_{50}) and exposure
- Help to link animal and human findings

- Provide guidance for designing clinical endpoint trials that use a rational dose range
- In some circumstances, characterize activity against different influenza types and subtypes
- Allow a clear weighing of benefit and risk at different doses

At present, it is not clear what exposure parameters or PD response parameters best predict anti-influenza efficacy outcomes. However, duration of viral shedding in nasal washes and clinical symptoms such as nasal congestion, feverishness, sore throat, cough, aches, fatigue, headaches, and chills/sweats are often measured. Typical influenza disease is restricted mostly to the respiratory tract and does not generally cause systemic viremia; however, there have been recent reports of isolation of A/H5N1 viral RNA from other organ system locations. Therefore, choice of virologic parameters for exposure-response analyses may depend on the influenza strain being studied. Sponsors are encouraged to discuss their choice of PD parameters with the FDA.

For detailed information on study design, see the guidances for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* and *Population Pharmacokinetics*, and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*.

2. Drug Development Population

Although influenza affects the entire population, phase 3 development plans can initially focus on treatment or prophylaxis of acute uncomplicated influenza in otherwise healthy individuals. However, sponsors also should conduct studies of persons at high risk of influenza complications such as the elderly, persons with underlying respiratory or cardiac disease, and immunocompromised persons who may not experience the same benefit or safety profile as otherwise healthy adults.

Influenza occurs worldwide with differing seasonality but often with similar viral strains causing outbreaks across continents. Because the timing and magnitude of outbreaks in a given location may be difficult to predict, influenza drug development programs can involve diverse geographic locations. Protocols with a range of both northern and southern hemisphere sites increase efficiency of drug development by allowing collection of data through different influenza seasons. When sponsors rely on foreign data, they should support the data with information about circulating influenza strains, patterns of clinical illness, study population demographics, standards of medical care, and use of other medical interventions in the countries where the studies were conducted. The relevance of foreign data to potential drug approval in the United States should be evaluated according to usual regulatory policy, with consideration of study conduct standards, study population demographics, availability of sites for inspection, and applicability of disease manifestations and usual medical care to that in the United States. Sponsors also can consult the guidance for industry *Acceptance of Foreign Clinical Studies*.

3. Efficacy Considerations

Efficacy studies for influenza treatment focus on symptom improvement in otherwise healthy persons with acute uncomplicated influenza. However, large studies in otherwise healthy

populations may not be appropriate for some drugs with major limiting safety concerns identified in earlier development.

In general, treatment and prophylaxis indications for influenza are different indications, and each indication should be supported by two adequate and well-controlled studies. However, sometimes a single persuasive study may be sufficient for each indication, depending on other supportive evidence.[7] Two trials that differ in design parameters and study populations are usually more useful than two identically designed trials or a single large trial. For example, one treatment study in adults and one treatment study in children is sufficient to support a treatment indication in adults and children. Additional studies in special populations can be used to extend and further define indications. Data from studies for different influenza-related indications (e.g., treatment of acute uncomplicated illness, treatment of severe illness requiring hospitalization, postexposure prophylaxis, and seasonal prophylaxis) can provide supportive safety and efficacy information to the extent appropriate based on dosing, duration of treatment, and populations studied.

The DAVP has received questions regarding indications for pandemic or avian influenza (as contrasted with seasonal influenza) or for a specific influenza subtype. In general, molecular targets of antiviral drugs have not been shown to be subtype-specific; however, resistant strains can emerge in different subtypes and within subtypes where other strains retain activity. Antiviral drug efficacy against novel strains with little or no population immunity and with virulence factors that differ from the strains studied in clinical trials may not be predictable, but some effect is likely if the molecular target remains sufficiently similar.[8] Information about strains circulating during a clinical trial is useful and should be collected and correlated with outcomes where possible.

Influenza development plans may be eligible for consideration under 21 CFR part 312, subpart E (Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses), fast track, or priority review if the specifics of the development plan justify such an approach. However, accelerated approval using surrogate endpoints under 21 CFR part 314, subpart H[9] has not been considered applicable to influenza drug development because clinical trials measure clinical benefit over a short time period and no surrogate marker has been reliably identified as reasonably likely to predict important clinical outcomes. For example, measurements of viral burden or shedding are not well-standardized or characterized in relation to clinical outcomes, and most patients clear virus with or without treatment. Exploratory analyses of viral burden

[7] The guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* addresses desirable study attributes for the use of a single study to support approval of a drug or a new indication.

[8] Some proposals for development may be based on strains predicted to interact with a specifically designed molecule such as antisense oligonucleotides, small interfering RNAs, and monoclonal antibodies. Given the propensity of known strains to antigenic drift, it is difficult to ensure that a planned intervention can be designed to bind only to a single specific portion of a predicted future pandemic strain protein or RNA. Usually, development is directed toward a conserved component of both circulating and hypothesized future pandemic strains, and it may be prudent to use mixtures of different antibodies or RNA segments to minimize escape mutations.

[9] The analogous accelerated approval provisions for therapeutic biologics are summarized under 21 CFR part 601, subpart E.

measurements, at relevant sites, and their relationship to clinical outcomes may contribute to future understanding of the relationships between viral levels in clinical specimens and clinical outcome.

The use of two or more antiviral drugs in combination may provide benefit greater than each drug alone in certain settings. Examples include treatment of serious life-threatening influenza illness with two drugs having synergistic or additive antiviral activity, or use of two drugs to delay emergence of resistance. However, combination treatment can result in increased toxicity and impractical dosing regimens, and/or hypothesized antiviral synergy might not occur to a clinically meaningful extent. Study designs should include provisions for demonstrating that each component of combination therapy contributes to the desired effect. Establishing the contribution of each component, generally using factorial designs, is important whether the proposed combination contains two or more antiviral drugs (e.g., a co-packaged combination, or a fixed-dose combination) or a combination of drug and therapeutic biological product. Sponsors should consult 21 CFR 300.50 for specific regulatory considerations regarding fixed-dose combinations.

4. Safety Considerations

Generation of a robust safety database from adequately blinded, well-controlled human studies in appropriate populations is important because of the wide variety of affected populations with a range of comorbidities that could interact with both disease and treatment. An application for a new influenza drug should include safety data from at least 1,500 patients at the dose and duration proposed for marketing. A safety database larger than 1,500 patients may be needed if early safety signals are identified in development. Drugs that are intended to affect host cells or host responses, rather than directly affecting the virus, may need additional assessment for unintended consequences of the host alterations.

Sponsors should provide a toxicity grading scheme for clinical trials. Commonly used schemata can be used (e.g., AIDS Clinical Trials Group, National Cancer Institute, or World Health Organization), with the understanding that toxicities with a relatively low grade assignment may be less acceptable in healthy populations commonly enrolled in influenza studies compared to populations at greater risk of serious disease outcomes, as observed in clinical trials of drugs for diseases such as cancer or human immunodeficiency virus.

B. Specific Efficacy Considerations for Phase 3 Trials

1. Study Design

a. Treatment studies: Acute uncomplicated influenza

Placebo-controlled studies are appropriate in settings and populations where the expected serious risk of nontreatment is small. Placebo-controlled rather than noninferiority designs, for studies evaluating treatment of uncomplicated mild to moderate influenza, should be used because the risks of receiving placebo are low and the efficacy of available treatment is modest (1-day difference in time-to-symptom improvement), variable, and cannot be predicted well enough to

support a noninferiority margin. The variable clinical course of influenza also makes uncontrolled data or historical controls difficult to interpret and inadequate to support efficacy of investigational drugs.

In addition to placebo-controlled studies, the following designs should be considered for influenza treatment studies: 1) superiority studies with approved antivirals as controls in otherwise healthy adults or children; 2) superiority studies with subjects receiving standard-of-care therapy (*usual care*) as controls in subjects with life-threatening influenza; and 3) dose-response (or concentration-response) studies where higher doses show significantly greater responses than lower doses.

It is possible that future influenza drugs may be approved with large enough effect sizes relative to placebo that they may in turn be used as active controls in noninferiority treatment studies.

b. Treatment studies: Serious influenza in hospitalized patients

The availability of treatments for serious influenza in hospitalized patients is an important public health concern. However, there are few studies of antiviral drugs in this setting and no approved influenza drug has definitively demonstrated clinical efficacy in serious influenza or hospitalized patients. Because there are no randomized studies showing efficacy of current antiviral drugs against serious influenza, an active-controlled noninferiority study is not possible. Despite the lack of studies showing benefit of antivirals in the treatment of serious influenza, we acknowledge investigator concerns about randomizing hospitalized patients with serious influenza to placebo. Consequently, the following are reasonable study design alternatives to a placebo-controlled design in serious influenza: 1) a randomized dose-response study, in which a significant dose response is demonstrated; and 2) a superiority add-on study, in which the combination of an investigational drug plus a *standard of care* is shown to be superior to a standard of care (such as a drug approved for uncomplicated influenza used *off-label* for the treatment of serious hospitalized influenza).

Because outbreaks of influenza are unpredictable and enrollment of serious or hospitalized patients probably will be more difficult than enrollment of uncomplicated cases, sponsors should consider collaborating with clinical trial networks with a wide range of sites.

c. Prophylaxis studies

Prophylaxis study designs include both: 1) interventions in communities after documentation of circulating influenza; and 2) household or institutional settings with documented exposure to a definite or clinically presumed case. Both sample size and risk-benefit assessments may be affected by the assumed intensity of exposure. For example, household or nursing home contacts may be at greater risk of disease than randomly recruited community dwellers. In settings in which there are definite recommendations from public health entities for drug prophylaxis (e.g., after onset of an outbreak within a nursing home), placebo controls will not be possible.

In populations in which prophylaxis is not considered necessary, standard-of-care, placebo-controlled trials can be considered. In prophylaxis studies, the rates of symptomatic infection in

placebo groups vary greatly depending on the season and population, and the absolute number of illness outcomes in any treatment group may be small. Vaccination status and changes in circulating viral strains also can have effects. The small number of outcomes and resulting large confidence intervals in a noninferiority comparison can make establishing the effect of a new drug difficult. For example, if two active drugs are compared and few or no cases of influenza illness are observed, this result can indicate similar effects of the two drugs or lack of a true influenza outbreak.

The most straightforward household influenza prophylaxis study design is when all symptomatic infected index cases receive the same care (i.e., all not treated with any active drug, all treated with the same study drug, or all treated with a specified alternative intervention). Households are then randomized to the investigational drug or control (e.g., placebo), such that all members of the same household receive the same assignment. This design does not provide information regarding whether treatment of the index case can itself decrease secondary transmission, nor does it provide information regarding potential interactions between the two interventions (e.g., reduction of prophylactic effect because of selection and shedding of resistant virus in the index case). A four-arm factorial-design study, in which index cases and household contacts are both randomized to treatment or placebo, can be used to answer questions regarding influenza transmission. Alternatively, sponsors can consider two or more separate studies with differing designs depending on the importance of each of these questions in the context of the specific drug.

2. Study Population

As mentioned, although influenza affects the entire population, phase 3 trials can initially focus on acute uncomplicated influenza in otherwise healthy individuals. However, sponsors also should conduct studies of persons at high risk of influenza complications such as the elderly, persons with underlying respiratory or cardiac disease, and immunocompromised persons who may not experience the same benefit or safety profile. We acknowledge that it can be a challenge to design studies for patients at risk; however, possible study design alternatives to placebo-controlled designs include dose-response studies, active-controlled superiority studies, combination versus single therapy studies, or single arm safety studies.

To fulfill Pediatric Research Equity Act requirements and extend treatment and/or prophylaxis indications to pediatric age groups, sponsors need to conduct well-controlled studies with clinical efficacy endpoints and complete safety evaluations.[10] PK and safety studies will not be considered adequate to extend the indications to pediatric age groups. Antiviral drug efficacy in children cannot be extrapolated from studies in adults because: 1) prior exposure and immunity typically present in adults may affect influenza illness and response to treatment differently than in children; and 2) viral shedding may differ in pediatric and adult age groups.

[10] See the Pediatric Research Equity Act.

3. Entry Criteria

For treatment studies, entry criteria should include documented influenza in the community and occurrence of clinical influenza-like symptoms, with laboratory confirmation generally not available at the time treatment is initiated.

Incorporation of a rapid test into entry criteria might lead to a more reliably influenza-positive population for analysis; however, all of the available tests have limitations, and the positive and negative predictive values of some rapid diagnostics may not be much better than clinical screening criteria during a seasonal epidemic. Novel influenza strains may have different test performance and different optimal sampling sites that may not be predictable from studies with previously circulating strains.

Vaccine status can be an entry criteria or a stratification factor and is likely to affect efficacy outcomes. A highly vaccinated population might impair the likelihood of showing treatment benefit by reducing the incidence and severity of illness in the control group or may actually enhance detection of treatment benefit if pre-existing immunity and drug treatment are additive or synergistic as some studies suggest. Antiviral drugs might theoretically have deleterious effects on response to live-virus influenza vaccine if they are administered in the same time period and inhibit replication of the vaccine virus; therefore, individuals who have recently received a live-virus vaccine generally should be excluded from participation. Drug effects in response to inactivated vaccine are less likely *a priori*. Careful documentation of vaccine status and performance of appropriate interaction analyses are important parts of study design, conduct, and interpretation.

4. Blinding

Double-blinding of treatments is important, given the subjectivity of endpoints and the potential for confusion between the natural variability of influenza and either beneficial or adverse effects of drugs.

5. Special Populations

Populations at high risk for influenza complications include the elderly and young age groups, pregnant women, and people with underlying medical conditions such as pulmonary disease, cardiac disease, and immunosuppressive conditions. In populations at risk of serious influenza complications for which a placebo-controlled study may be considered undesirable, we recommend dose-response studies or superiority studies against an active control or standard of care to allow for efficacy comparisons.

Because disease outcomes, vulnerability to adverse drug events, and overall risk-benefit considerations may differ in high-risk groups relative to the general population, sponsors should consider plans for obtaining safety and efficacy information in special populations. These plans should be discussed early in the development process and revised as information becomes available to guide such studies. Information obtained from studies in special populations also can provide insights into possible events in the general population in a pandemic setting. For

example, studies in populations with little immunity to influenza and high or prolonged viral replication, as reported in young children and immunocompromised patients, may provide useful information about likely patterns of resistance emergence and relations between dose or duration of treatment and outcomes in a pandemic setting.

6. Dose Selection and Route of Administration

Animal studies, challenge studies, and dose-ranging studies in naturally occurring influenza disease can all contribute to dose selection for pivotal clinical trials. Exposure-response relationships can be assessed in all of these settings, and PD parameters, such as those relating to viral clearance, can be explored. As previously noted, we strongly recommend that sponsors conduct adequate phase 2 studies before designing the phase 3 trials.

For some drugs, more than one route of administration can be considered, and different dosing, safety, and efficacy issues may arise with different routes of administration. For example, an oral form may be desirable for uncomplicated influenza while an intravenous formulation may be more desirable for seriously ill patients who may not be able to take oral formulations. For inhalation routes, determination of dosing for clinical trials based on nonclinical data can be challenging. In addition, if a novel strain is associated with viral replication in a broader range of organ systems than usual seasonal influenza, an inhalational route may be insufficient. The safety of drugs delivered by inhalational routes should be evaluated in subjects with pre-existing pulmonary disease, with appropriate safety precautions and monitoring, because individuals with pulmonary disease may be at highest risk for both influenza complications and adverse reactions caused by inhalational drugs.

The use of an antiviral drug with an inhalation device for delivery is subject to 21 CFR part 3, which provides procedures for determining which FDA center has primary jurisdiction for a combination drug product with components potentially subject to review in different centers. Generally, combination drug products are regulated through the Center for Drug Evaluation and Research (CDER) because the drug represents the primary mechanism of action of the product. Drug review can involve consultation and collaboration across divisions or centers depending on specific attributes of each component. The sponsor of a proposed combination drug product should ensure that adequate information is provided about the device as well as the drug in such a combination, including any proprietary information that may be needed for review. If there are questions about which center has primary jurisdiction, a determination can be requested at the time of initiating interactions with the FDA.

7. Efficacy Endpoints

a. General considerations

Endpoints can involve combinations of objective measurements, evaluations by health care professionals, and patient-reported symptoms. Efficacy endpoints have not been definitively standardized for all types of influenza studies; however duration of defined influenza symptoms has been used in registrational studies of acute uncomplicated influenza. We have recently initiated reassessment of the approach to patient-reported components of outcome

measurements.[11] Because of the variability of influenza illness and drug effects in past studies, most clinical trials warrant examination of multiple secondary endpoints to show consistency of effect with the primary endpoint. Rationale for both primary and secondary endpoints should be included in protocol submissions and discussed prospectively.

For both treatment and prophylaxis designs, virologic measurements are important secondary endpoints and can be used as components of study entry criteria or evaluability. Viral assays also contribute to laboratory confirmation of endpoints in prophylaxis trials. Identification of specific viral subtypes and strains also can be valuable for secondary analyses. Development of methodology for quantitative cultures at relevant sites, and for assessment of relationships between viral burden (including asymptomatic shedding) and secondary transmission, should be explored.

Concomitant use of symptomatic relief medications may add to the difficulty of endpoint evaluation, but probably is not avoidable. Confounding caused by concomitant medicines may be lessened if protocols standardize and measure their administration.

Assessments of influenza complications will be important if sponsors propose claims of reduction in complications. Objective criteria should be delineated and justified prospectively whenever possible, and information on the specifics of diagnosis and management should be collected in the protocol.

b. Treatment of acute uncomplicated illness

The primary endpoint in acute uncomplicated influenza treatment studies in adults should be the time to a defined level of symptom improvement. Components of the primary endpoint include fever plus a constellation of symptoms (e.g., cough, coryza, headache, body aches, sore throat). Secondary clinical endpoints should be time to return to normal activity and time to resolution of fever or other individual symptom included in the primary endpoint.

Sponsors should propose and provide justification for a standardized and/or well-studied instrument for symptom measurement. We discourage adding scores for different symptom types into an aggregate score or area under the curve of symptoms, and consider these analyses exploratory because of the difficulty of equating units of severity of different symptoms.

The primary analysis population should include all subjects with confirmed influenza (intent-to-treat (ITT) infected), but additional analyses also should include all study subjects (ITT population). Exploratory analyses of *on-treatment* or *per-protocol* populations may be valuable to identify problems with dosing approaches or instructions.

[11] See the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

c. Seriously ill hospitalized patients

For seriously ill influenza patients requiring hospitalization, proposed endpoints have included signs and symptoms, duration of hospitalization, requirements for supplemental oxygen or assisted ventilation, and mortality. Choice of endpoint may vary depending on the clinical setting and/or viral strains. A single best endpoint has not been identified in seriously ill hospitalized patients, and proposals should be provided for advance discussion. Duration of viral shedding is an important secondary endpoint that may be useful in phase 2 studies for comparing doses or selecting doses for phase 3 studies.

d. Prophylaxis

The primary endpoint for prophylaxis studies should be the occurrence of symptomatic, laboratory-confirmed influenza. Symptom diaries plus serology and targeted cultures or nucleic acid amplification tests (NAATs) have been used to identify laboratory-confirmed cases of symptomatic influenza. Additional analysis of all subjects with influenza-like symptoms (with or without laboratory confirmation) can be a useful secondary endpoint but may reflect noninfluenza illnesses with symptoms similar to influenza that are not susceptible to anti-influenza drugs and would presumably reduce effect size.

Studies should be designed so that an appropriate range of secondary analyses can be performed to allow overall conclusions on the totality of the data. Analysis of all subjects with laboratory evidence of influenza infection, which counts both symptomatic and asymptomatic subjects as *prophylaxis failures*, can be a valuable secondary endpoint. However, the relevance of preventing asymptomatic infection is unclear, since the goal of influenza prophylaxis is to prevent symptomatic illness, and not just laboratory-identified seroconversion. On the one hand, it may be preferable to avoid infection altogether because asymptomatically infected persons might shed and transmit virus despite the presence of the prophylactic drug. On the other hand, asymptomatic infection may offer protection against illness if a new exposure occurs after stopping a prophylactic drug.

In addition to the usual primary objective of preventing symptomatic influenza illness, there is interest in ascertaining whether disease is milder in persons who develop influenza illness while receiving prophylaxis compared to persons not receiving prophylaxis. This outcome may be difficult to assess in most prophylaxis studies because of relatively low numbers of breakthrough cases with active drugs. However, if appropriate collection of symptom information is prospectively included during protocol planning, such severity-of-illness comparison can be a useful analysis to include in study design.

e. Reduction in complications

Findings and symptoms that are part of influenza illness should not be considered separately as complications if they are more properly part of a multicomponent principal endpoint. If *complications requiring antibiotics* are proposed among the study endpoints, the bacterial complication should fit prospectively defined criteria and appropriate expert guidelines for a bacterial infection requiring antibiotics. For example, many clinical diagnoses of sinusitis or

bronchitis may be part of the clinical spectrum of influenza itself and may not fit practice guidelines for antibacterial treatment. We encourage sponsors to propose prospective definitions of potential serious outcomes (even those outcomes expected to occur with low frequency and therefore not likely to have sufficient event numbers for primary analysis) to perform appropriate secondary analyses.

8. Study Procedures and Timing of Assessments

Intensive clinical assessment is important in the period shortly after treatment initiation in treatment studies and presumed exposure in prophylaxis studies. The typical self-limited disease course may limit the ability to see treatment effects at later time points. Prophylaxis and treatment studies should include long enough follow-up to detect symptom recurrence after temporary improvement, late adverse events, or emergence of resistant virus. Protocols should include frequent self-assessments, with observer assessment at less frequent intervals or as triggered by self-assessment results.

Available in vitro diagnostic tests for influenza use multiple methods ranging from research laboratory procedures to marketed test kits, and require anywhere from minutes to days for completion. Marketed test kits for influenza are regulated in the Center for Devices and Radiological Health (CDRH), and include several *rapid tests* designed to detect viral antigens or enzyme activity within 30 minutes.[12] Ability to obtain specific types of diagnostic specimens, and to obtain a positive result in the setting of infection, may vary with factors such as severity of disease, age, timing, collection technique, and characteristics of novel viral strains such as principal anatomic distribution and sites of viral replication. Currently, FDA-cleared rapid diagnostic tests for influenza can be labeled as detecting influenza A, influenza A and B without distinguishing between types, or detecting and distinguishing between influenza A and B. One subtype-specific NAAT for H5N1 has been recently cleared. Tests labeled for influenza A (or A and B) may detect a number of subtypes in analytic testing, but clinical experience is limited to subtypes and strains circulating at the time trials were conducted.

Diagnostic and monitoring assays used in a clinical trial but not FDA-cleared through CDRH are considered investigational. Drug sponsors should provide sufficient information on methodology and performance to allow evaluation of the appropriateness of the assay for its proposed purpose. Use of an investigational assay in a clinical trial does not constitute FDA approval or endorsement of the assay. If a diagnostic assay proposed for use in a clinical trial has not been previously cleared by the FDA but eventually may be developed for commercial distribution, the sponsor should consider early discussions with CDRH as well as CDER, to facilitate collaborative or consultative review and comment as appropriate.

[12] CDRH regulates in vitro diagnostic tests for influenza and has published the guidances for industry and FDA staff *In Vitro Diagnostic Devices to Detect Influenza A Viruses: Labeling and Regulatory Path* (http://www.fda.gov/cdrh/oivd/guidance/1594.html) and *Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Influenza Viruses* (http://www.fda.gov/cdrh/oivd/guidance/1638.html) on development of influenza diagnostics, and a Laboratory Safety Tip, *Cautions in Using Rapid Tests for Detecting Influenza A Viruses* (http://www.fda.gov/cdrh/oivd/tips/rapidflu.html), that discusses cautions in the use of rapid influenza tests that can detect influenza virus antigens or viral enzyme activity within 30 minutes.

In studies designed to evaluate the efficacy of an anti-influenza drug for treatment, viral influenza cultures (nose and/or throat swabs or nasal wash) should be performed at baseline (before dosing) and at intervals during and after treatment. Duration of viral shedding is a valuable secondary endpoint but may be difficult to calculate if cultures are performed infrequently. Measurement of anti-influenza antibodies should be performed at baseline and during follow-up, preferably about 4 weeks after diagnosis. Serology should use standardized methodology, and supporting information for the assay should be provided in advance. Seroconversion response to influenza antigens is assessed as an increase by a factor of 4 or greater, to assist in evaluating influenza diagnosis in treatment studies and as part of the outcome definition of laboratory-confirmed symptomatic influenza in prophylaxis studies. Therefore, it is important to assess whether an antiviral drug interferes with antibody response once infection is established (to avoid confounding effects in treatment studies), and to evaluate the extent of effects on seroconversion in prophylaxis studies.

Subtyping and genotyping may be important for exploration of relationships to intervention effects, and also for identification of sources of viral transmission in studies of prophylaxis and transmission prevention. Baseline susceptibility and emergence of resistance to the study drug should be examined in clinical trials (across the range of potential study designs). If well-standardized and generally accepted susceptibility testing methods are not available, samples should be saved for future testing. In some instances, more than one approach to susceptibility testing may be warranted. For example, enzyme inhibition assays may be useful in screening samples but may yield different results from virus yield assays, and both may be important for assessment of resistance. Sponsors should consult existing guidance on virology studies and submission of resistance data for aspects relevant to influenza.[13]

Interactions between vaccines and antiviral drugs may warrant consideration in some study designs. Timing of serum samples to assess seroconversion should be carefully considered to distinguish between antibody responses to vaccine and infection-related seroconversion as a diagnostic confirmation.

Detailed viral resistance monitoring plans describing proposed analyses, sample collection times, assay characteristics with different influenza types and subtypes, and assay methodologies should be provided for review early in development, and updates discussed at appropriate intervals during development. The issue of relative *fitness* of resistant viruses should be approached with great caution, given the complexity of potential determinants of infectivity and virulence, and the potential for multiple mutations with diverse and sometimes compensatory consequences.

9. Statistical Considerations for Phase 3 Studies

Sponsors should provide a protocol with a statistical analysis plan (SAP) for review and the protocol with the SAP should be finalized with FDA concurrence before subject enrollment.

[13] See the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency* and its attachment *Guidance for Submitting Influenza Resistance Data* (http://www.fda.gov/cder/guidance/index.htm).

686 a. Treatment studies
687
688 The primary endpoint in acute uncomplicated influenza illness treatment studies in adults should
689 be the time to a defined level of symptom improvement. The primary efficacy analyses should
690 focus on the population with laboratory-confirmed influenza, a baseline characteristic even if not
691 defined until after baseline. Analyses of safety should be based on all randomized subjects given
692 the likelihood that treatment decisions in clinical practice would be made before confirmation of
693 diagnosis.
694
695 The unit of randomization and analysis in such studies is the individual study subject. We
696 recommend stratification by time since onset of symptoms when there is a sufficiently wide
697 window for enrollment to make this stratification meaningful. Consideration of other possible
698 stratification variables also can be worthwhile when a study is to be conducted in a
699 heterogeneous population in which specific characteristics such as viral strain, smoking status,
700 location, or the use of nonprescription symptom relief medication or other concomitant
701 treatments might affect the natural history of illness or the magnitude of treatment effect.
702
703 Sponsors should avoid censoring subjects in the ITT infected population in these short-term
704 trials. There should be an explicit plan to deal with missing data.
705
706 b. Prophylaxis studies
707
708 In prophylaxis studies, the primary endpoint should be the occurrence of symptomatic,
709 laboratory-confirmed influenza.
710
711 Examples of populations that can be enrolled in prophylaxis studies, each with its own design
712 and analysis considerations, include: households, communities of healthy adults, and nursing
713 homes.
714
715 • **Households.** Households with multiple members in the appropriate age categories
716 should be identified and screened in advance. When an index case is reported in a
717 screened household, that household should be randomized to one treatment arm. There
718 are three possible designs, as follows:
719
720 1. Index cases are untreated and all contacts in a household are randomized to the same
721 treatment, either placebo or study drug
722 2. Index cases are treated and all contacts in a household are randomized to placebo or
723 study drug
724 3. Factorial studies with four arms are conducted that include all four combinations of
725 index cases (treated or untreated) and contact cases treated or untreated:
726
727 – Index treated and contacts given prophylaxis
728 – Index treated and contacts given placebo
729 – Index untreated and contacts given prophylaxis
730 – Index untreated and contacts given placebo
731

The second design is a less powerful test of prophylaxis than the first design if treating the index case reduces the risk to the contact cases. The third design is recommended if one wishes to describe both benefit of index case treatment on contact case risk and the benefit of contact case prophylaxis.

In household studies, the entire household is both the randomized unit and the unit of analysis. The primary efficacy analysis should compare the treatment groups for the percentage of households in which there was at least one randomized contact case that developed symptomatic, laboratory-confirmed influenza. In other words, if one contact case in the household becomes symptomatically infected, the household is counted as infected. If none of the contact cases become infected, the household is considered not infected. Secondary analyses also can compare the percentage of contact cases that had symptomatic, laboratory-confirmed influenza in the active and placebo treatment groups.

Designs in which different contact cases in the same household receive different regimens raise the concern of drug sharing and introduce more problems with intrahousehold correlation. Similarly, analyses with individual contact cases as the unit of analysis also may introduce the same kind of problems. Stratification on size of household can be used but is not expected to produce any consequential increase in power.

- **Communities of healthy adults.** For community studies with healthy adults (e.g., college campuses), subjects should be screened at the beginning of the flu season and randomized to control or test prophylaxis arms when there is occurrence of a predefined epidemiological signal that an influenza epidemic is underway in the target community, or in a larger community (e.g., the county containing the college campus).

- **Nursing homes.** For studies in nursing homes, screening, randomization, and analysis should be similar to that for communities of healthy adults. Nursing home studies should involve more careful definition and monitoring of clinical endpoints because subjects may lack mental acuity for self-assessment and staff will have many aspects of all subjects' health to monitor. These latter concerns apply to treatment studies in nursing homes as well.

  In studies of prophylaxis in nursing homes and other community dwellings, the unit of randomization and the unit for analysis is the individual study subject.

Statistical power in prophylaxis studies depends on the number of protocol-defined endpoint outcomes (symptomatic laboratory-confirmed infection) and the effect size of the intervention, not on the number of subjects enrolled. Therefore, the sample size of prophylaxis studies should be based on the number of such outcomes expected and a cautious estimate of effect size. Because incidence of influenza varies unpredictably from year to year, the number of subjects in a community prophylaxis study during one flu season may yield fewer than the number of influenza illnesses expected. It is advisable to monitor total number of influenza cases to see whether numbers are fewer than expected. Continuation of the study into a second flu season is appropriate if influenza attack rates are low, even if not initially specified in the protocol. There

should be no unblinding of results at the end of the first season if the total number of influenza illnesses is still inadequate at that point.

For prophylaxis studies, principal analyses and power calculations can be based on the odds ratio or relative risk comparing the prophylaxis failures (symptomatic, laboratory-confirmed influenza) for the study treatment arms. Because failures tend to be few in the active prophylaxis arms, exact statistical procedures should be used instead of normal approximations for inferences.

Minimizing missing data is important in studies that have a small number of treatment outcomes. Investigators should be diligent in obtaining the final status of subjects either on or off the assigned treatment, either in the study or if terminated from the study. If a subject does not come back for evaluation after the sponsor has exhausted all reasonable means to persuade the subject to do so, the following information should be collected and documented: the subject's status (e.g., ascertain whether alive), a description by the subject and his or her contacts on the flu symptoms and adverse events, and the general well-being of the subject.

Subjects with diary cards that are missing data for several days (i.e., less than 1 week) or subjects with negative laboratory confirmation who miss their follow-up serology assessment should be considered to have missing data. Subjects with missing data in community and nursing home studies are counted as not having symptomatic laboratory-confirmed influenza. A household with no confirmed cases of influenza that has at least one contact case withdraw from the study should be defined as a household with missing data. Households with missing data and no identified influenza cases are counted as not having symptomatic laboratory-confirmed influenza in the primary analysis.

Because prophylaxis failures are defined based on flu symptoms and laboratory confirmation with viral assays, the source of these symptoms and the performance of these assays will have an effect on the observed failures and, therefore, on the study power and analysis. The assay specificity (i.e., the assay's ability to classify a sample as negative when it is truly negative) is likely to have the most influence. The use of a highly specific and sensitive assay or assays is of great importance in increasing study power.

Sponsors must ensure that pertinent investigational records such as diary data and copies of original laboratory sheets are retained so that they are available at the time of any FDA inspections (21 CFR 312.62(c)).

10. Accelerated Approval (Subpart H) Considerations

The regulations in 21 CFR part 314, subpart H (accelerated approval based on a surrogate endpoint considered reasonably likely to predict clinical benefit in patients with a serious or life-threatening disease)[14] have not been used for approval of influenza antivirals, and are unlikely to be appropriate in most instances, because usual clinical trials involve direct assessment of

[14] Similar considerations apply to therapeutic proteins or monoclonal antibodies that might be proposed for development under the analogous biologics regulations in 21 CFR part 601, subpart E.

immediate clinical outcomes for an acute uncomplicated illness. In addition, virologic parameters have not been shown to reliably predict clinical outcomes in influenza studies.

11. Risk-Benefit Considerations

The balance between potential risks and benefits of influenza interventions should be considered throughout the development process and are taken into account in many of the subtopics of this guidance. Risk-benefit considerations are likely to be affected by the status of public health need (e.g., severity of an influenza epidemic or pandemic, virulence of circulating influenza strains, epidemiology of illness and complications, availability of vaccine) and by the status of supplies and apparent effect of other available anti-influenza drugs.

C. Other Considerations

1. Relevant Nonclinical Safety Considerations

In general, we anticipate that the nonclinical toxicology studies for influenza drugs will be similar to studies for other antimicrobial drugs. One question often asked about influenza drugs is whether animal toxicology data to support chronic administration are needed. Although influenza treatment is usually short-term and prophylaxis often no more than a few weeks, the possibility of multiple courses of treatment or prophylaxis over a series of influenza seasons should be taken into account in determining the nature and duration of nonclinical safety studies. For instance, if the indication for a drug is treatment of influenza, long-term carcinogenicity studies in rodents usually are not needed. If, on the other hand, the drug is indicated for the prophylaxis of influenza, carcinogenicity studies in rats and mice should be carried out before approval because drugs used frequently in an intermittent manner in the treatment of chronic or recurrent conditions generally should be supported by such studies. The ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* provides detailed information concerning the conditions under which carcinogenicity studies should be conducted.

2. PK and PD Considerations

a. PK measurement

Several administration routes have been considered for influenza drugs: oral, parenteral, inhalation, and intranasal. For oral and parenteral administration, plasma drug concentrations are presumed to be correlated with concentrations at site of action, although prediction of clinical effect cannot be assumed even in this setting. However, for inhalation and intranasal administration in prophylaxis or in treatment of typical influenza, drug concentrations at the epithelial layer of trachea, bronchi, bronchioles, and lung may better correlate with the antiviral activity. Avian influenza or novel influenza strains may have a tendency to replicate outside the respiratory system, necessitating systemic exposure of an antiviral agent.

Concentrations in the nasal cavity, respiratory tract, and lung can be estimated from nasal wash, sputum (by sputum induction), and bronchioalveolar lavage, respectively. Imaging also can be

applied during influenza drug development. Technetium-99 scintigraphy is a technology currently used to quantify the percentage of dose or mass of drug deposited in the lungs, oropharynx, and nasopharyngeal cavity after inhalation or nasal drug delivery. The main purpose of the technetium-99 scintigraphy study is for selection of devices, formulations, and administration routes during drug development. Fluorescent imaging (e.g., flurine-19 imaging) may estimate concentrations in the respiratory tract. All of the above methods are somewhat exploratory and have not been shown to be directly suitable for regulatory purposes such as labeling or approval decisions. However, comparing concentrations in a targeted organ to cell culture EC_{50} values or antiviral activity data from animals with similar concentrations in a targeted organ may help select doses for clinical studies.

b. PD measurement

Virologic response or clinical endpoints can be used as response metrics in the exposure-response evaluations. Viral titer in nasal wash has been used as a measure of virologic response; however, viral titer reduction in nasal wash should not be used as a primary endpoint supporting drug approval. For prophylaxis trials, the clinical endpoint should be used (i.e., percentage of subjects developing symptomatic laboratory-confirmed influenza during prophylaxis). Relationships between each of these assessments and the principal efficacy endpoints should be assessed based on all available data.

Viral samples from the throat and rectum can be analyzed for sporadic human infections with avian influenza strains, because avian influenza viruses generally show highest affinities for α-2-3 linked sialic acid, which is the dominating receptor type in epithelial tissues of gut and lung in influenza-infected birds. In addition, there have been recent human avian influenza case reports of gastroenteritis without respiratory symptoms.

Any drug exposure-related toxicity should be explored to assess the relationship of exposure to the adverse event, to define the highest tolerable exposure, and to determine the probability of an adverse event with a given exposure. This information can also guide dose adjustments for special populations.

c. Modeling considerations

Exposure response modeling of phase 2 and/or phase 3 data should be included in a new drug application (NDA) to characterize relationships between drug concentrations and efficacy and safety. Data from cell cultures, animal studies, and from studies of other drugs from the same class should be considered when an exposure-response model is developed. Disease progression and response in a placebo group should be incorporated in the modeling. Demographic data (e.g., sex, race, age, body weight, and vaccination status) should be collected and incorporated into the exposure-response model. To increase understanding of exposure-response relationships, we recommend collection of viral genotype information to assess relationships between genetic variants (genotypes), exposure, and response outcomes, such as, but not limited to, drug response, efficacy, safety, toxicity, and overall survival. If measurable baseline factors are deemed to be clinically significant covariates, dose adjustment and individualization may need to be considered.

3. Labeling Considerations

Patient labeling is important for influenza drugs because of the possibility of extensive use by persons unfamiliar with the drugs. Whether a patient package insert or MedGuide is considered for this purpose depends on the extent of safety concerns and the specific circumstances expected for use. If the drug may be purchased for stockpiling, see section III.C.6., Stockpiled Drug Products, for labeling issues related to stockpiled drugs.

4. Animal Rule (Subpart I) Considerations

Because of intense interest in the use of animal models for influenza drug development, this section discusses several specific uses of animal data.

Data from animal studies can provide supporting information for human study design or, in some cases, can provide supportive information contributing to regulatory decisions. Together with ongoing clinical trial development plans, animal data also can facilitate access to investigational drugs under IND or emergency use authorization (EUA) mechanisms. However, because human clinical trials in influenza are feasible, ethical, and the best approach for characterizing safety and efficacy, the Animal Rule (21 CFR 314, subpart I, or corresponding biologics regulations 21 CFR 601, subpart H) is not an appropriate mechanism for approval of influenza drugs. Animal models in general have not been fully characterized or reliably predictive for influenza. Even though the value of clinical trial data of previous strains for predicting outcomes for novel strains is uncertain, it is not clear that animal data with a new prevalent strain would be superior to that of clinical data of previous strains. In addition, a strain used in animal studies may differ substantially from the strain that subsequently causes widespread human illness or a pandemic. Thus, treatment trials in virus-challenged animals are not a substitute for clinical trials.

5. Emergency Use Considerations

To prepare for use of antiviral drugs in a pandemic situation, sponsors of approved or investigational antiviral drugs are encouraged to prepare protocols that might be adaptable in a pandemic and that can be rapidly finalized and implemented in an emergency. Reasons for advance preparation of protocols for use in an emergency situation include:

- Advance consideration of protocols may help to facilitate emergency readiness and data collection.
- Protocols may benefit patients in an emergency by guiding clinical decisions about the continuation or modification of treatment interventions.
- Protocols may support revisions of other ongoing protocols or development of future protocols.
- Protocols may help to avoid continued diversion of resources into use of investigational interventions that subsequently show lack of efficacy or unacceptable toxicity.
- Protocols may enhance understanding of other potentially important interventions as the pandemic extends through its phases.

- Protocols may remind health care professionals of dose adjustments and basic safety follow-up that can contribute to patient management and draw attention to major new safety or resistance concerns that can improve management of subsequent patients.
- Data from a protocol in an emergency situation may help to support future regulatory actions.

When designing protocols, sponsors should consider collection of natural history information for illness caused by a novel strain, flexible designs to encompass widespread mild or severe disease, and incorporation of monitoring and stopping rules to facilitate study modification as more is learned about a novel viral strain and associated disease.

The Project BioShield Act (Public Law 108-276) permits the FDA to authorize the use of an unapproved drug or the unapproved use of an approved drug in an actual or potential emergency during the effective period of a declaration of an emergency. An EUA may be issued for a specific drug if the totality of available scientific evidence indicates that it may be effective for diagnosing, preventing, or treating a serious or life-threatening disease or condition.[15] We anticipate that drugs considered for use under an EUA will have substantially more data than that required to support administration to subjects under an early IND protocol so that an appropriate risk-benefit evaluation can be made to decide whether an EUA is justified.

If a drug can be considered for an EUA, advance submission and review of protocols with supporting information can contribute to evaluation of the authorization. Although protocol changes may be warranted after initial information about the emergency situation is assessed, preparation of basic protocols in advance of need will facilitate expert discussion and review, preparation for situational flexibility while preserving study integrity, and initial discussions of institutional review board and consent processes.

In most instances, the route toward use of a drug under an EUA includes nonclinical and clinical studies directed toward influenza drug development. Information from studies in animal models, or human challenge studies, in combination with other human clinical trial data appropriate to the development stage contribute to the evaluation of an EUA proposal. If a potential EUA requestor believes consideration of EUA status is warranted, the potential requestor is encouraged to contact the FDA as early as possible and to provide data in support of such consideration.

Although INDs and EUAs might be considered either for new antiviral drugs or for new uses of existing drugs, the amount of new information needed may differ depending on prior experience with the drug, as well as factors such as intended population (e.g., treatment of gravely ill patients without other treatment options versus prophylaxis of low-risk persons likely to have good outcome without treatment).

[15] See the guidance *Emergency Use Authorization of Medical Products* (http://www.fda.gov/oc/guidance/emergencyuse.html).

6. Stockpiled Drug Products

Approved drugs, or investigational drugs with sufficient safety and efficacy data to consider widespread investigational use, can be considered for stockpiling by appropriate entities. We do not make decisions regarding selection or purchase of drugs for stockpiling. However, we will review sponsor proposals for stockpile-specific manufacturing, labeling, and packaging. Information collected during initial studies can be used to develop simplified instructions for potential use during a pandemic. The instructions on the container label may need to be assessed for clarity based on the anticipated distribution modes and whether it will be possible to provide additional instructions (e.g., during a pandemic it may not be possible for a health care professional to supply appropriate counseling). The inclusion of tear-off panels with lot information for record keeping purposes may be useful in some stockpile situations. Sponsors who wish to propose stockpile-related packaging or instructions should provide information about concerns from potential purchasers that affect their packaging or labeling proposals. Documentation should be provided to show how the submitted proposal addresses priorities expressed by specified potential purchasers and how the purchasers together with the sponsor plan to manage any pitfalls associated with the proposed packaging or instructions. For additional packaging issues for stockpiled drugs, see section III.C.7., CMC Considerations.

7. CMC Considerations

We anticipate that the chemistry, manufacturing, and controls (CMC) data for influenza drugs will be comparable to the CMC data for other drugs with similar uses and administration,[16] although allowances could be made (e.g., reduced or modified expectation for stability data) in situations of dire need. Special CMC considerations may arise for drugs intended for stockpiling. For example, because the distribution of stockpiled drugs during a pandemic may take place rapidly and under less than ideal conditions, it may be advantageous to package such drugs in configurations that can be readily dispensed. This type of packaging can include drugs in unit-of-use bottles instead of bulk packs that require a pharmacist to dispense the appropriate number of tablets or capsules. Similarly, stockpiled drugs that are not taken orally might be packaged in kit configurations that include all associated paraphernalia such as diluents, syringes, needles, and delivery devices to facilitate quick drug delivery in remote conditions or under emergency conditions. Assembly of such a kit from separately stored components may not be feasible during a pandemic situation. Another factor that can be considered is the use of packaging presentations that can be readily relabeled if the expiration dating period of the stockpiled drug is extended (e.g., the use of bottles instead of blister packages).

If specific packaging configurations are developed, they should be described clearly and a scientific justification should be provided for their selection. Stability studies should adequately address all climate zones where the drug may potentially be stockpiled. Temperature cycling

[16] General guidance pertaining to CMC of drug development can be found on the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm. We strongly recommend a quality-by-design approach to drug development, as well as the principles described in the draft ICH guidances for industry *Q8(R1) Pharmaceutical Development* and *Q10 Pharmaceutical Quality System* and the ICH guidance for industry *Q9 Quality Risk Management*.

1039 studies and humidity variation studies should be carried out to support temperature excursions
1040 and humidity changes that are typically encountered during stockpiling.
1041

REFERENCES[17]

Guidances relevant to general safety and efficacy determinations

Draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*

Guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*

Guidance for industry *Acceptance of Foreign Clinical Studies*

Guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

Guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials*

ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*

Guidances relevant to clinical pharmacology and exposure-response assessments

Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*

Guidance for industry *Population Pharmacokinetics*

Guidances relevant to nondrug influenza interventions (vaccines and diagnostics)[18]

Draft guidance for industry and FDA staff *Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Influenza Viruses* (http://www.fda.gov/cdrh/oivd/guidance/1638.html)

Guidance for industry *Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines* (www.fda.gov/cber/gdlns/panfluvac.htm)

[17] These guidances can be found on the CDER guidance Web page at http://www.fda.gov/cder/guidances/index.htm unless otherwise noted.

[18] In addition to these guidances, see the CDRH Laboratory Safety Tip, *Cautions in Using Rapid Tests for Detecting Influenza A Viruses* (http://www.fda.gov/cdrh/oivd/tips/rapidflu.html).

Guidance for industry *Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines* (http://www.fda.gov/cber/gdlns/trifluvac.htm)

Guidance for industry and FDA staff *In Vitro Diagnostic Devices to Detect Influenza A Viruses: Labeling and Regulatory Path* (http://www.fda.gov/cdrh/oivd/guidance/1594.html)

Guidance for industry and FDA staff — Class II Special Controls Guidance Document: *Reagents for Detection of Specific Novel Influenza A Viruses* (http://www.fda.gov/cdrh/oivd/guidance/1596.html)

Guidances relevant to virologic measurements

Guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency* and its attachment *Guidance for Submitting Influenza Resistance Data*

Guidances relevant to expediting review processes and access to investigational drugs in settings of public health need

Guidance *Emergency Use Authorization of Medical Products* (http://www.fda.gov/oc/guidance/emergencyuse.html)

Guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review* (http://www.fda.gov/cber/gdlns/fsttrk.htm)