Guidance for Industry

Influenza: Developing Drugs for Treatment and/or Prophylaxis

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

April 2011
Clinical Antimicrobial

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the 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 trials and nonclinical studies to support the development of influenza drug products.[3] This guidance includes discussions on the following topics:

- Nonclinical development
- Early phases of clinical development
- Phase 3 protocol designs and endpoints for the treatment of both uncomplicated and serious influenza

[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 (i.e., 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 (i.e., 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.

- Protocol designs for prevention of symptomatic influenza
- The role of animal data in an influenza drug development program
- Considerations relating to the potential for emergency use of influenza drugs, including advance development of protocols for further exploration and verification of drug effects under epidemic and pandemic conditions

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 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 drug 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*.[4]

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 trials in illness caused by circulating influenza virus strains. Approved antiviral drugs for influenza fall into two classes, neuraminidase inhibitors and the adamantanes.

Influenza infections can produce a wide spectrum of clinical illness ranging from a self-limited febrile illness with respiratory symptoms to severe disease with complications sometimes

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

resulting in hospitalization and death. The severity of influenza depends on the virus strain and host, and is not always predictable at an individual level. To date, antiviral drugs have shown the ability to modestly reduce symptoms in *uncomplicated* or otherwise self-limited illness. Currently, no antiviral drug has been shown to definitively reduce serious complications, hospitalization, or mortality in a randomized clinical trial. Although this guidance addresses approaches to studying both self-limited and serious influenza, most regulatory experience involves trials in the treatment of *uncomplicated illness* (i.e., self-limited illness treated at home without secondary complications) and prophylaxis.

Concerns about the possibility of pandemic spread of novel influenza strains have led to increased interest in influenza drug development;[5] however, seasonal influenza remains a major public health concern. Because of their close relationship, seasonal and pandemic influenza are considered together in the 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, as noted below:

- 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 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 a potential pandemic, it is difficult to predict which strain might emerge as a source for a pandemic. In addition, substantial additional genetic change is likely as a novel strain progresses from sporadic to pandemic. The difficulty in predicting the emergence of pandemic strains is illustrated by the recent antigenically novel reassortant strain of a previously circulating subtype (previously referred to as swine-origin influenza virus), which caused the first influenza pandemic of the 21st century.[6]

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

[6] The 2009 pandemic strain of the H1N1 subtype differs antigenically from the H1N1 that has circulated in humans for decades; is reported to be most closely related but not identical to H1N1 strains that have circulated in swine, containing genes of swine, avian, and human origin; and has not been detected in nonhuman hosts before the emergence of human outbreaks in 2009. The new strain also illustrates the lack of predictable correspondence between subtype and antiviral susceptibility, having emerged with a pattern of resistance mutations more similar to the seasonally circulating H3N2 than to the then most recent circulating H1N1 strains in human populations.

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 or in sporadic cases caused by other novel strains. In addition, changes in seasonal strains, including emergence of resistance, can decrease drug effectiveness over time. Thus, information on potential differences in drug responsiveness among strains or subtypes, including novel strains isolated from human infections, should be explored by generating and assessing additional data from cell culture and animal studies, and by collecting and analyzing 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 the influenza drug development are of great interest. Development pathways can be designed to provide information supporting access to investigational drugs if public health emergency arises 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 can 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 trials 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 antiviral activity in cell culture assays and, on the basis of those assay results, for in vivo activity in appropriate animal models of influenza infection.[7] Sponsors may need to assess the potential of their candidate drugs to enhance replication of other pathogens that mimic or complicate influenza, including other respiratory viruses and bacteria associated with similar illnesses or complications.

Although not a regulatory requirement or replacement for clinical trials, cell culture and animal studies can: (1) make valuable contributions to clinical trial designs, including dosing

[7] The National Institutes of Health (National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases, Virology Branch) has an antiviral drug screening program designed to help identify potentially active antiviral drugs, including those to treat influenza. Information about this program and related activities can be accessed at http://www.niaid.nih.gov/topics/viral/Pages/Default.aspx.

considerations and resistance monitoring plans; (2) assist in exploring the generalizability of clinical trial results; and (3) be used to:

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

Proposals for animal studies should include supporting information on the selection, justification, and characterization of the animal 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, dose and timing effects, and available information linking animal data to human exposure-response and outcomes.

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

a. Phase 2A: Challenge trials

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

Challenge trials can provide useful exposure-response and safety information, as well as an opportunity to demonstrate pharmacological antiviral activity in humans under controlled conditions outside the influenza season. Data from challenge trials can contribute to dose selection for phase 2B and phase 3 trials, and provide the opportunity to explore the effects of different times of drug initiation relative to virus exposure. However, challenge trials should not be considered efficacy trials that can be used to support marketing approval, because challenge strains typically produce a milder set of symptoms compared to naturally occurring influenza, and inoculation in challenge trials may differ from acquisition in naturally occurring infections (e.g., amount of inoculum in challenge trials could be larger or smaller at various mucosal sites

compared to naturally occurring infections). In addition, challenge trial 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 can vary from those recognized in well-characterized challenge strains.

Whether challenge trials are feasible is dependent on the availability of adequately safety-tested challenge strains and ethics considerations. Proposals for challenge trials should include documentation of the safety testing and biologics investigational new drug application (IND) status (in CBER) of the influenza challenge strains. It is important for a sponsor wishing to use any new challenge strains to coordinate and consult with CBER staff reviewing the IND. The use of 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 trials on the basis of animal and human PK and tolerability data, cell culture EC_{50} values (adjusted for protein binding), animal model PK/PD data, and any other relevant information.

b. Phase 2 dose-ranging trials

The design of phase 2 dose-ranging trials depends on the type of population for phase 3 trials, as well as the phase 1 safety profile of the investigational drug. We recommend that sponsors conduct phase 2 trials before designing phase 3 trials. Proceeding directly to phase 3 from phase 1 or phase 2A trials may fail to produce useful phase 3 data, especially if selection of doses and regimens are not scientifically justified. Phase 2 dose-ranging trials usually are designed with adequate statistical power to detect differences in viral shedding (e.g., duration, quantitative differences from baseline), as well as differences in clinical symptoms that 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 trials are one type of adequate and well-controlled trial that, if appropriate clinical endpoints in appropriate populations are measured, can contribute to substantial evidence of effectiveness (21 CFR 314.126). In addition, exposure-response trials and their analyses can provide support for approval of different doses, dosing regimens, or dosage forms. Depending on the trial endpoints, exposure-response information can:

- Help to connect cell culture 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
- Characterize activity against different influenza types and subtypes
- Allow a risk-benefit analysis at different doses

At present, it is not clear what PK exposure parameters or PD response parameters best predict anti-influenza efficacy outcomes. However, duration of viral shedding in nasal washes is often measured, together with clinical symptoms such as nasal congestion, feverishness, sore throat, cough, aches, fatigue, headaches, and chills/sweats. Typical influenza disease is restricted

mostly to the respiratory tract and does not generally cause systemic viremia; however, there are occasional reports of isolation of viral RNA (e.g., A/H5N1) from other organ systems. 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 in a clinical development meeting during phase 1 or phase 2.

For detailed information on trial design, see the guidance 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, we recommend that sponsors conduct trials in: (1) persons at high risk of influenza complications, such as the elderly; (2) persons with underlying respiratory or cardiac disease; and (3) immunocompromised persons who may not experience the same benefit or safety profile as otherwise healthy adults. Such trials should be conducted as soon as appropriate data permit initiation of trials in these populations.

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 clinical trial data — whether as part of multinational trials including the United States or as part of trials conducted entirely outside the United States — to support the marketing approval of their candidate drugs, they should supplement the foreign data with information about circulating influenza strains, patterns of clinical illness, trial population demographics, standards of medical care, and the use of other medical interventions in the countries where the trials were conducted. Sponsors should evaluate the relevance of foreign data under applicable FDA regulations, with considerations of trial conduct standards, trial population demographics, availability of sites for regulatory inspection, and applicability of disease manifestations and the standard medical care compared to that in the United States. Sponsors also can consult the guidance for industry *Acceptance of Foreign Clinical Studies* and the final rule "Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application."[8]

3. Efficacy Considerations

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

[8] See 73 FR 22800, April 28, 2008 (revising 21 CFR 312.120).

populations may not be appropriate for some drugs if major limiting safety concerns have been 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 trials. However, sometimes a single persuasive trial may be sufficient for each indication, depending on other supportive evidence.[9] Two trials that differ in design parameters and populations usually are more useful than two identically designed trials or a single large trial. For example, one treatment trial in adults and one treatment trial in children may be considered sufficient to support a treatment indication in adults and children. Additional trials in special populations can be used to extend and/or further define indications. Data from trials 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.

With regard to indications for pandemic or avian influenza (as contrasted with seasonal influenza) or for a specific influenza subtype, molecular targets of antiviral drugs in general have not been shown to be subtype-specific. However, resistant strains can emerge in different subtypes and within the same subtype. It may not be possible to predict antiviral drug efficacy against novel strains with little or no population immunity or strains with virulence factors that differ from the strains studied in clinical trials. However, some drug effect is likely if the molecular target remains sufficiently similar.[10] Information about strains circulating during a clinical trial is useful and should be collected and correlated with clinical 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,[11] is not applicable to influenza drug development because clinical benefits are assessed 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 clinical status generally can be measured at least as frequently and as rapidly as virologic status. In addition, most

[9] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* for characteristics of a single adequate and well-controlled clinical trial that can contribute to a conclusion that such trial would be adequate to support an effectiveness claim.

[10] Some proposals for drug 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.

[11] See also 21 CFR part 601, subpart E, for the accelerated approval provisions for therapeutic biologics for serious or life-threatening illnesses.

patients clear virus with or without treatment, and the magnitude and timing of treatment-related changes in viral shedding has not been clearly associated with clinically meaningful changes in disease resolution. Exploratory analyses of viral burden measurements at relevant sites and their relationship to adequately monitored and measured clinical outcomes may contribute to future understanding of the relationships between viral levels in clinical specimens and clinical outcome.

Although using two or more antiviral drugs in combination might provide greater therapeutic benefit than using each drug alone in certain settings, such added value of combination therapy has yet to be established for influenza. Combination therapy, particularly with drugs from different classes, can potentially result in synergistic or additive antiviral activity, or prevent or delay emergence of resistance. Combining drugs also can be useful in cases where circulating viruses of different types or subtypes are known to harbor resistance-associated substitutions, and there are no readily available point-of-care tests capable of distinguishing between virus types or viruses with substitutions. In this situation, the objective of the combination is to provide initial treatment for each of the major diagnostic possibilities, rather than to enhance treatment effect against a specific virus.

However, combination treatment can result in increased toxicity and impractical dosing regimens. In addition, hypothesized antiviral synergy might not be clinically meaningful. Therefore, trial designs should demonstrate the activity of each component of combination therapy (i.e., contribution of each component to the combination).[12] 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 drug and a therapeutic biological product. Sponsors should consult 21 CFR 300.50 for specific regulatory considerations regarding fixed-dose combinations.

4. Safety Considerations

It is important to develop a robust safety database from adequate and well-controlled human trials in appropriate populations because a wide variety of affected populations with a range of comorbidities could interact with both disease and treatment. An application for initial approval of a new influenza drug for the treatment of uncomplicated influenza 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 have been identified in development. Drugs that are intended to affect host cells or host responses, rather than directly affecting the virus, may need additional safety assessments (including special laboratory evaluations as appropriate for the agent) on more patients for unintended consequences of the host alterations. For new drugs showing important clinical benefit in serious influenza in hospitalized patients, an initial safety database of approximately 500 patients at the dose and duration proposed for treatment use may be sufficient for filing a marketing application for the treatment of serious influenza.

[12] See the draft guidance for industry *Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Sponsors should provide a toxicity grading scheme for clinical trials. For trials of influenza prophylaxis or treatment of uncomplicated influenza, we recommend toxicity scales appropriate for use in healthy volunteers.[13] For treatment of serious influenza or treatment of influenza in patients with underlying medical conditions, other toxicity grading scales can be used (e.g., those adopted by the AIDS Clinical Trials Group, National Cancer Institute, or the World Health Organization).

B. Specific Efficacy Considerations for Phase 3 Trials

1. Trial Design

a. Treatment trials: Acute uncomplicated influenza

Placebo-controlled trials are appropriate in settings and populations where the expected serious risk of nontreatment is small.[14] For trials evaluating treatment of uncomplicated mild to moderate influenza, placebo-controlled rather than noninferiority designs 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 an adequate noninferiority margin. The variable clinical course of influenza in any given season, as well as the potential for differences in pathogenicity and host immunity as new influenza strains emerge and change over time, also makes uncontrolled data or historical controls difficult to interpret and inadequate to support efficacy of investigational drugs.

In addition to placebo-controlled trials, the following designs should be considered for acute uncomplicated influenza treatment trials: (1) superiority trials with approved antivirals and/or symptomatic treatment as active controls in otherwise healthy adults or children; and (2) dose-response (or concentration-response) trials 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 trials.

b. Treatment trials: Serious influenza in hospitalized patients

From a public health perspective, it is important to have treatments available for serious influenza in hospitalized patients. However, there are few trials of antiviral drugs in this setting. In addition, because no trial has definitively demonstrated substantial clinical efficacy of an

[13] See the guidance for industry *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*.

[14] Some public health authorities may not recommend routine treatment of influenza with currently approved antivirals because of concerns about risk-benefit, including the risk of resistance emergence.

antiviral drug in serious influenza or in hospitalized patients,[15] determination of a noninferiority margin is not possible. As a result, an active-controlled noninferiority trial is not possible.[16]

Despite the lack of definitive randomized trials showing a specific magnitude of benefit of antivirals in the treatment of serious influenza, we acknowledge investigator concerns about randomizing hospitalized patients with serious influenza to placebo alone. Consequently, sponsors can consider the following reasonable trial design alternatives in serious influenza: (1) a randomized and blinded dose-response (or duration-response) trial, in which a significant dose response is demonstrated; and (2) a superiority add-on trial, 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). Showing efficacy differences in dose-response trials and superiority trials is challenging if all treatment arms are believed to have similar benefit. Adequate frequency and intensity of patient assessments are important to maximize the likelihood of detecting potential, clinically relevant differences.

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. Trial design proposals should delineate how the proposed design (including sample size and power) will be able to detect an effect of the investigational drug on improving the patients' clinical status.

c. Prophylaxis trials

Prophylaxis trial designs include interventions in communities after documentation of circulating influenza, and household or institutional settings with documented exposure to a definite or clinically presumed case. Both sample size and risk-benefit assessments of such trials 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 trials, the rates of symptomatic infection in placebo groups vary greatly depending on the season and population, and the number of illness outcomes in any treatment group may be small. Vaccination status and changes in circulating viral strains also may effect the number of symptomatic cases observed. The small number of

[15] A limited number of observational and case-control studies have reported various types of clinical benefit of antivirals for serious influenza; however, the margin of benefit was modest (both clinically and statistically). There were also questions about the reliability of the data because of potential biases when comparing treated and untreated groups. Observational comparisons between presumed active treatments, or between different times of treatment initiation, also have major risks of bias, compromising the ability to derive reliable estimates of effect size from such comparisons.

[16] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

outcomes and resulting large confidence intervals in a noninferiority comparison can make it difficult to establish the effect of a new drug. 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, which would make it difficult to conclude the two drugs have similar effects.

We consider the most straightforward household influenza prophylaxis trial design to be when: (1) all symptomatic infected index cases receive the same care (i.e., none is treated with any active drug, or all are treated with the same candidate drug, or all are treated with a specified alternative intervention); and (2) households are then randomized to the investigational drug or control (e.g., placebo), such that all members of the same household receive the same drug or control. This design does not provide information regarding whether treatment of the index case can itself decrease secondary transmission, or the potential interactions between the two interventions (e.g., reduction of prophylactic effect because of selection and shedding of resistant virus in the index case). To answer questions regarding influenza transmission, a four-arm factorial-design trial can be used in which index cases and household contacts are both randomized to treatment or placebo. Alternatively, sponsors can consider two or more separate trials with differing designs depending on the importance of each of these questions in the context of the specific candidate drug.

2. Trial Population

As mentioned previously, 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 trials enrolling persons at high risk of influenza complications, such as the elderly, individuals with underlying conditions such as respiratory or cardiac disease, and immunocompromised persons (e.g., HIV-infected patients, organ transplant recipients, or patients receiving cancer chemotherapy). These patients may not experience the same benefit or safety profile from the candidate drug when compared with other patient populations. It can be a challenge to design trials for patients at risk. Possible trial design alternatives to placebo-controlled designs include but are not limited to dose-response trials, active-controlled superiority trials, combination versus single therapy trials, and single-arm or active-controlled safety trials.

In addition, trials in populations with little immunity to influenza and high or prolonged viral replication (e.g., young children and immunocompromised patients) may provide useful information about potential patterns of resistance emergence and relationships between the treatment dose or duration and clinical outcomes. In trials of serious influenza, we encourage enrollment of patients with influenza-related complications, such as those needing intensive care support or mechanical ventilation.

To fulfill the Pediatric Research Equity Act requirements and extend treatment and/or prophylaxis indications to pediatric age groups, sponsors need to conduct adequate and well-controlled trials with clinical efficacy endpoints and complete safety evaluations.[17] PK and safety trials will not be considered adequate to extend the indications to children, particularly

[17] See the Pediatric Research Equity Act.

those younger than 12 years of age. Antiviral drug efficacy in children cannot be extrapolated from data generated from trials 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.

Sponsors can include adolescents in adult trials as appropriate, depending on an individual candidate drug's pharmacologic characteristics.

3. Entry Criteria

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

Incorporation of a *rapid test* into the entry criteria might lead to a more reliably influenza-infected population for analysis (as later confirmed by polymerase chain reaction (PCR), culture, or serologic titres). However, all of the currently available rapid tests have limitations, and the positive and negative predictive values of some rapid tests may not be much better than those of clinical screening criteria during a seasonal epidemic. Novel influenza strains may have different test performance and/or different optimal sampling sites that may not be predictable from trials with previously circulating strains. We recommend enrollment based upon clinical symptoms followed by confirmation with a sensitive and specific RT-PCR diagnostic assay at a central laboratory.

Vaccination status can be an entry criteria or a stratification factor, and is likely to affect efficacy outcomes. The likelihood of detecting treatment benefit in a highly vaccinated population may be decreased because the incidence and severity of illness may be reduced. However, such likelihood may be increased if pre-existing immunity and drug treatment are additive or synergistic, as some trials suggest. Antiviral drugs might theoretically have deleterious effects on response to a live-virus influenza vaccine if they are administered in the same time period as the vaccine and inhibit replication of the vaccine virus. Therefore, individuals who have recently received a live-virus influenza vaccine generally should be excluded from participation. Drug effects in response to inactivated vaccine are less likely. Documentation of vaccination status and performance of appropriate statistical interaction analyses are important parts of trial design, conduct, and interpretation.

For prophylaxis trials, entry criteria generally should be broad and reflect the population intended for use. Most trials will be conducted in otherwise healthy adults. Trials can be designed to look at families, college students, or perhaps individuals with underlying health conditions in institutionalized settings (e.g., nursing homes).

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 the drug effects (either beneficial or adverse).

5. Dose Selection and Route of Administration

Animal studies, challenge trials, and dose-ranging trials 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. PD parameters, such as those relating to viral clearance, also can be explored. As previously noted, we strongly recommend that sponsors conduct adequate phase 2 trials before designing the phase 3 trials.

For some drugs, more than one route of administration can be considered, which may result in different dosing, safety, and efficacy issues. For example, an oral form may be desirable for uncomplicated influenza, whereas an intravenous formulation may be more desirable for seriously ill patients who may not be able to take oral formulations. For inhalational routes, it can be challenging to determine appropriate dosing for clinical trials based on nonclinical data. In addition, if a novel strain is associated with viral replication in a broader range of organ systems than the usual seasonal influenza, an inhalational route may be insufficient to have an antiviral effect in organs other than the lungs and respiratory tract. 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 inhalational device for delivery is subject to the FDA regulations at 21 CFR part 3, which provide procedures for determining which FDA center has primary jurisdiction for a combination product with components potentially subject to review in different centers. Generally, combination products are regulated through the Center for Drug Evaluation and Research (CDER) because the drug component represents the primary mechanism of action of the product. Drug review can involve consultation and collaboration across divisions or centers depending on the specific attributes of each component. The sponsor of a proposed combination product should ensure that adequate information is provided to the FDA 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.[18]

6. Efficacy Endpoints

a. General considerations

Efficacy 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 trials; however, duration of defined influenza symptoms has been used in registrational trials of acute uncomplicated influenza. There have been recent advances in endpoint assessment using patient-reported components of outcome

[18] For more information, contact the Office of Combination Products (http://www.fda.gov/CombinationProducts/default.htm).

measurements.[19] Because of the variability of influenza illness and drug effects in previous trials, 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 with the FDA.

For treatment trials, virologic measurements are important secondary endpoints and can be used as components of entry criteria or evaluability. Currently, we do not consider virologic endpoints to be appropriate primary endpoints in phase 3 treatment trials because: (1) there is no established predictive relationship between magnitude and timing of viral reductions and extent of clinical benefit of how a patient "feels, functions, or survives"; (2) optimal sampling site, methods including collection procedures, and assays for clinically relevant virologic measurements have not been established; and (3) available data suggest substantial variability in results and conclusions using different methods for collecting and analyzing virologic data.

In addition, unlike trials in HIV and hepatitis C virus, influenza clinical outcomes occur in the same time frame as virologic changes. Therefore, using virologic endpoints does not shorten trial duration. Previous influenza trials do not suggest that virologic endpoints would provide a quicker or easier way to distinguish between therapies than direct measurements of clinical outcome. Thus, even if more evidence can be collected regarding the predictive value of virologic measurements, such measurements would not necessarily reduce the trial size or duration, although they could further contribute to secondary analyses.

Viral assays also contribute to the laboratory confirmation of endpoints in prophylaxis trials. Identification of specific viral subtypes and strains also can be valuable for secondary analyses. Sponsors should explore the development of methodology for quantitative cultures and quantitative RT-PCR at relevant sites, and for assessment of relationships between viral burden (including asymptomatic shedding) and secondary transmission. Sponsors should also provide assay performance data with currently circulating strains to support the use of the proposed assays in their trials.

In trials of acute uncomplicated influenza, concomitant use of symptomatic relief medications may make the endpoint evaluation more difficult. Confounding caused by concomitant medicines may be mitigated if protocols are standardized to measure their administration. Alternatively, a standardized regimen of symptom relief medication (e.g., acetaminophen) may be used as an active comparator to an influenza antiviral drug in a superiority design trial.

If sponsors propose claims of reduction in complications, objective criteria should be delineated and justified prospectively. Information on the specifics of diagnosis and management should be collected in the protocol.

b. Treatment of acute uncomplicated illness

The primary endpoint in treatment trials in adults for acute uncomplicated influenza should be the time to a pre-defined level of symptom improvement. Components of the primary endpoint

[19] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

should include fever with a constellation of symptoms (e.g., cough, coryza, headache, body aches, sore throat). This clinical symptom endpoint is not considered a surrogate endpoint because it measures clinically relevant symptoms associated with influenza. For treatment of acute illness in otherwise healthy individuals, demonstrating reductions in secondary complications or mortality is not necessary for an antiviral to be considered clinically useful. Secondary clinical endpoints should be time to return to normal activity, and time to resolution of fever, and/or other individual symptoms included in the primary endpoint. The emergence of drug resistance is an important tertiary endpoint in all influenza trials.

Sponsors should provide justification for a standardized and/or well-accepted instrument for symptom measurement. We discourage adding scores for different symptom types into an aggregate score or *area under the curve* of symptoms. We consider these analyses exploratory because it is difficult to equate the units of severity of different symptoms.

The population for both the primary analysis and additional analyses should include all subjects with confirmed influenza (i.e., intent-to-treat (ITT) infected population). Exploratory analyses of *on-treatment* or *per-protocol* populations may be used to identify problems with dosing approaches or instructions.

c. Treatment of seriously ill hospitalized patients

For seriously ill influenza patients requiring hospitalization, a primary endpoint should include clinical signs and symptoms, duration of hospitalization, time to normalization of vital signs and oxygenation, requirements for supplemental oxygen or assisted ventilation, and mortality. Choice of endpoint may depend on the clinical setting and/or viral strains. A single best endpoint has not been identified in seriously ill hospitalized patients, and clinical trial proposals should be provided for advance discussion. Sponsors are encouraged to provide evidence for the ability of their proposed endpoint to directly measure how a patient feels, functions, or survives, taking into account all relevant documentation from literature sources and clinical trials. Such endpoint is intended to demonstrate whether the candidate drug produces a more rapid and/or more complete improvement in the condition of the patient compared to the control. Further developmental work to evaluate the most relevant clinical endpoint for assessing benefit in trials of serious influenza treatment is needed and strongly encouraged.

d. Prophylaxis

The primary endpoint for prophylaxis trials should be the occurrence of symptomatic, laboratory-confirmed influenza. Symptom diaries, along with 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. However, such approach may include noninfluenza illnesses with symptoms similar to influenza that are not susceptible to anti-influenza drugs, and would presumably reduce the effect size.

We recommend a secondary analysis that compares the prophylactic effect of all subjects (both symptomatic and asymptomatic) with laboratory evidence of influenza infection. However, the

clinical benefit of preventing asymptomatic infection is unclear, because the goal of influenza prophylaxis is to prevent symptomatic illness, and not just asymptomatic 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 subjects have stopped taking a prophylactic drug.

In addition to the primary objective of preventing symptomatic influenza illness, there is interest in ascertaining whether disease is milder in persons who develop it while receiving prophylaxis compared to persons not receiving prophylaxis. This outcome may be difficult to assess in most prophylaxis trials because of the relatively low numbers of breakthrough cases among individuals receiving active antiviral drugs. However, if appropriate collection of symptom information is prospectively included during protocol planning, such severity-of-illness comparison can be a useful analysis for potentially supporting additional statements in product labeling.

e. Reduction in complications

Findings and symptoms that are part of influenza illness should not be considered separate complications if they are part of a multicomponent principal endpoint. Bacterial infection complications should meet pre-defined criteria according to appropriate expert guidelines. For example, a clinical diagnosis of bronchitis may be part of the clinical spectrum of influenza itself, and may not meet the criteria for a secondary bacterial infection. We encourage sponsors to propose prospectively definitions of potential serious outcomes for secondary analysis, including those outcomes expected to occur with low frequency and therefore not likely to have sufficient event numbers for primary analysis. Methods of diagnosis and confirmation of secondary infections should be described in detail in the protocol and be consistent across all trial sites. Diagnoses of secondary complications should be confirmed by objective clinical, laboratory, and medical imaging findings as appropriate. In the absence of such objective confirmation, labeling statements regarding efficacy claims for the prevention of secondary complications are unlikely.

7. Trial Procedures and Timing of Assessments

Intensive clinical assessment is important in the period shortly after treatment initiation in treatment trials and presumed exposure in prophylaxis trials. The typical self-limited disease course may limit the ability to detect treatment effects at later time points. Prophylaxis and treatment trials should include sufficiently long follow-up to detect symptom recurrence after temporary improvement, late adverse events, or emergence of resistant virus. Protocols should include frequent self-assessments (e.g., use of diary cards), along with observer assessments at less frequent intervals or as triggered by self-assessment results. Self-assessments should continue until resolution of all clinical signs and symptoms. For trials in hospitalized patients, some aspects of clinical assessment may be suitable for frequent measurement, and/or may be routinely recorded in hospital medical records and available for analysis, especially during the initial period of acute illness. Self-reporting of symptoms may become more important in patients who are improving but still symptomatic.

Available in vitro diagnostic tests for influenza, ranging from research laboratory procedures to marketed test kits, use multiple methods, and require anywhere from minutes to days to complete. Marketed test kits for influenza are regulated by the Center for Devices and Radiological Health (CDRH), and include several rapid tests designed to detect viral antigens or enzyme activity within 30 minutes.[20] The ability to obtain specific types of diagnostic specimens, and to achieve the desired test sensitivity and specificity in the setting of infection, may vary with factors such as severity of disease, patient age, treatment timing, collection technique, and characteristics of novel viral strains, such as principal anatomic distribution and sites of viral replication. Currently, FDA-cleared rapid tests for influenza can be labeled as detecting influenza A, detecting influenza A and B without distinguishing between the two 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. However, clinical experience is limited to the subtypes and strains circulating at the time when trials supporting the FDA clearance of the tests were conducted.

Although results would likely not be available at trial entry, we recommend inclusion of a sensitive and specific assay (e.g., real-time RT-PCR assay) for laboratory confirmation of influenza infection to assist in defining the infected population for trial analyses in influenza treatment trials.

We consider diagnostic and monitoring assays that are used in a clinical trial but have not been cleared by the FDA to be investigational. Drug sponsors should provide sufficient information on the methodology and performance of such assays to allow the FDA to evaluate the appropriateness of the assays for their intended use. Use of an investigational assay in a clinical trial does not constitute FDA clearance 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.

In trials designed to evaluate the efficacy of an anti-influenza drug for treatment, viral influenza cultures (i.e., nose and/or throat swabs or nasal wash) should be performed at baseline (before dosing) and at appropriate intervals during and after drug treatment. Duration of viral shedding is a valuable secondary endpoint but may be difficult to determine if cultures are performed infrequently. Measurement of anti-influenza antibodies should be performed at baseline and

[20] CDRH regulates in vitro diagnostic tests for influenza and has published the following guidances for industry and FDA staff on its Web site at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm: *In Vitro Diagnostic Devices to Detect Influenza A Viruses: Labeling and Regulatory Path* and *Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Influenza Viruses* on development of influenza diagnostics (when final, this guidance will represent the FDA's current thinking on this topic), and a Laboratory Safety Tip, *Cautions in Using Rapid Tests for Detecting Influenza A Viruses* (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm109356.htm), that discusses cautions in the use of rapid influenza tests that can detect influenza virus antigens or viral enzyme activity within 30 minutes.

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 confirming influenza diagnosis in treatment trials, and as part of the outcome definition of laboratory-confirmed symptomatic influenza in prophylaxis trials. Therefore, it is important to assess whether an antiviral drug interferes with antibody response once infection is established in treatment trials and to evaluate the extent of effects on seroconversion in prophylaxis trials.

Subtyping and genotyping may be important for exploration of relationships between viral type and treatment, and for identification of sources of viral transmission in trials of prophylaxis. Baseline susceptibility and emergence of resistance to the trial drug should be examined in clinical trials, regardless of trial designs. If standardized and generally accepted susceptibility testing methods are not available, samples should be retained for future testing until the trial has been completed and data have been analyzed. 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 generate different results from virus yield assays; yet both may be important for the assessment of drug resistance. Recent trials have shown higher rates of resistance to influenza drugs when a clonal analysis is employed. We recommend that resistance be evaluated early in development to better inform phase 3 protocol design. Sponsors should consult existing guidance on virology studies and submission of resistance data for aspects relevant to influenza.[21]

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

Sponsors should provide detailed viral resistance monitoring plans that describe proposed analyses, sample collection timing, assay characteristics with different influenza types and subtypes, and assay methodologies. Such plans should be provided to the FDA for review early in development, and updates to the plans should be 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.

8. Statistical Considerations for Phase 3 Trials

Sponsors should provide a protocol with a statistical analysis plan for review for FDA concurrence before subject enrollment.

[21] 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*.

a. Treatment trials

The primary efficacy analyses should focus on the population with laboratory-confirmed influenza, a baseline characteristic even if it is not defined until after baseline data are collected. The primary endpoint in treatment trials in adults for acute uncomplicated influenza illness should be the time to a pre-defined level of symptom improvement. Analyses of safety data should be based on all randomized subjects given the likelihood that treatment decisions in clinical practice would be made before confirmation of diagnosis.

The unit of randomization and analysis in such trials is the individual trial subject. We recommend stratification by time since onset of symptoms when there is a sufficiently wide window for enrollment to make this stratification meaningful. Consideration of other possible stratification variables also can be useful when a trial is to be conducted in a heterogeneous population in which specific characteristics such as viral strain, smoking status, location, or the use of nonprescription symptom relief medication or other concomitant treatments might affect the natural history of illness and/or the magnitude of treatment effect.

Sponsors should avoid censoring subjects in the ITT infected population in these short-term trials. There should be an explicit and adequate plan to address issues relating to missing data.

b. Prophylaxis trials

In prophylaxis trials, the primary endpoint should be the occurrence of symptomatic, laboratory-confirmed influenza.

Examples of populations that can be enrolled in prophylaxis trials, each with its own design and analysis considerations, include households, communities of healthy adults, and nursing homes.

- **Households.** Households with multiple members in the appropriate age categories should be identified and screened in advance. When an index case is reported in a screened household, that household should be randomized to one treatment arm. There are three possible designs, as follows:

  1. Index cases are untreated and all contacts in a household are randomized to the same treatment, either placebo or candidate drug

  2. Index cases are treated and all contacts in a household are randomized to different treatments, which could be placebo or candidate drug

  3. Factorial trials with four arms are conducted that include all four combinations of index cases (treated or untreated) and contact cases (treated or untreated):

     – Index treated and contacts given prophylaxis (with candidate drug)
     – Index treated and contacts given placebo
     – Index untreated and contacts given prophylaxis (with candidate drug)
     – Index untreated and contacts given placebo

The second design is a less powerful test of prophylaxis than the first design if treating the index case reduces the risk of influenza infection to the contact cases. The third design is recommended if one wishes to assess the benefit of: (1) index case treatment on contact case risk; and (2) contact case prophylaxis.

In household trials, 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 at least one randomized contact case 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 becomes 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 concerns of drug sharing and intrahousehold correlation. Analysis using individual contact cases as the unit of analysis also may cause similar problems. Stratification on the size of household can be used, but is not expected to produce any consequential increase in power.

- **Communities of healthy adults.** For community trials with healthy adults (e.g., trials conducted in 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 where the college campus is located).

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

  In prophylaxis trials in nursing homes and other community dwellings, the individual trial subject is both the unit of randomization and the unit of analysis.

Statistical power in prophylaxis trials depends on the number of protocol-defined endpoint outcomes (i.e., symptomatic, laboratory-confirmed infection) and the effect size of the intervention, rather than the number of subjects enrolled. Therefore, the sample size of prophylaxis trials should be based on the number of such outcomes expected and a conservative estimate of effect size. Because incidence of influenza varies unpredictably from year to year, the number of subjects in a community prophylaxis trial during one flu season may yield fewer than the expected number of influenza illnesses. We recommend monitoring total number of influenza cases to determine whether it is lower than expected. It is appropriate to continue the

trial into a second flu season if influenza attack rates are low, even if such continuation was 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 trials, principal analyses and power calculations can be based on the odds ratio or relative risk comparing the prophylaxis failures (i.e., symptomatic, laboratory-confirmed influenza) between the 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 prophylaxis trials 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, regardless of whether they are in the trial or have been terminated from the trial. 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., whether alive or not), a description by the subject and his or her contacts of the subject's flu symptoms and adverse events, and the general well-being.

Subjects with diary cards that are missing data for several days (i.e., less than 1 week) and 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 trials are counted as not having symptomatic, laboratory-confirmed influenza in the primary analysis. A household with no confirmed cases of influenza that has at least one contact case withdrawn from the trial 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 trial 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 (such as RT-PCR) is of great importance in increasing trial power. Sponsors should provide a detailed description of the assay's methodology and supporting sensitivity and specificity data with isolates representing the diversity of influenza viruses.

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

9. Accelerated Approval (Subpart H) Considerations

The criteria described in 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)[22] have not been used for approval of influenza antivirals, and are unlikely to be appropriate in most instances, because typical influenza clinical trials involve direct assessment of immediate clinical outcomes for an acute uncomplicated illness. In addition, virologic parameters have not been shown to reliably predict clinical outcomes in influenza trials. If situations arise in which sponsors wish to propose development under accelerated approval regulations, the proposals submitted for discussion and feedback should address the issues related to efficacy assessment and endpoint selection outlined in other sections of this guidance, and should also indicate how the subpart H requirements for subsequent clinical endpoint confirmation of benefit would be fulfilled.

10. Risk-Benefit Considerations

The balance between potential risks and benefits of influenza interventions has been discussed elsewhere in this guidance, and should be considered throughout the influenza drug development process. Risk-benefit considerations are likely to be affected by the public health need (e.g., severity of an influenza epidemic or pandemic, virulence of circulating influenza strains, epidemiology of illness and complications, and availability of vaccine), the status of antiviral drug and vaccine supplies, and the apparent effect of other available anti-influenza drugs. Emergence of drug resistance and viral strain susceptibility should also be part of risk-benefit assessments.

C. Other Considerations

1. Relevant Nonclinical Safety Considerations

Although influenza treatment is usually short-term and prophylaxis often lasts 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

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

effect cannot be assumed 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 drug's antiviral activity. Avian influenza or novel influenza strains may have a tendency to replicate outside the respiratory system, necessitating systemic exposure of an antiviral drug.

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 a technetium-99 scintigraphy study is to select devices, formulations, and administration routes during drug development. Fluorescent imaging (e.g., fluorine-19 imaging) may estimate drug 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 drug 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 trials.

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 primary 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.[23] If additional novel strains of influenza (of avian or other origin) show other patterns of viral distribution, other sample types might be considered if appropriate.

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.

[23] Beigel, JH, 2005, Avian Influenza A (H5N1) Infections in Humans, N Engl J Med, 353-1374-85.

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 trials 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 into 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 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 should be 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) and Animal Model Considerations

Because of the 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 trial design or, in some cases, supportive information contributing to regulatory decisions (see examples in section III.A.1., Nonclinical and Early Phase Clinical Development Considerations). 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, and corresponding biologics regulations in 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 shown to be reliably predictive for influenza. Even though the value of clinical trial data of previous strains in predicting outcomes for novel strains is uncertain, it is not clear that animal data with a new prevalent strain would be more useful than 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 Access Considerations

a. IND use

To prepare for use of antiviral drugs in a potential public health emergency, we encourage sponsors of approved or investigational antiviral drugs to prepare protocols that might be adaptable in a pandemic or other emergency setting and that can be rapidly finalized and implemented in a form appropriate to the circumstances. These protocols should be designed both to guide use of the drug and to collect data that can contribute to improvements in use, including support for assessment of both efficacy and safety wherever appropriate. However, given the conditions under which the drug may be administered in these protocols, protocol design should be simple and streamlined to answer a few relatively simple questions. Reasons for advance preparation of such protocols for use in an emergency situation include:

- Advance consideration of protocols may help 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 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 suitably designed protocol in an emergency situation may help 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 trial modification as more is learned about a novel viral strain and associated disease.

b. Emergency use authorization

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.[24] 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.

In most instances, the route toward use of a drug under an EUA includes both nonclinical studies and clinical trials directed toward influenza drug development. Information from studies in animal models, or human challenge trials, in combination with other human clinical trial data appropriate to the development stage, contribute to the evaluation of an EUA proposal. EUA proposals should contain sufficient information to justify dosing regimens and potential for antiviral activity and clinical benefit, and to evaluate potential risks. In EUA proposals, it is also important to consider dosing recommendations for populations such as children, pregnant women, and individuals with renal insufficiency that may be at higher risk of influenza complications. 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, to provide data in support of such consideration, and to engage in pre-EUA interactions with the FDA. Such interactions can identify additional types of information that might be important to support the EUA consideration. Use of a drug under an EUA is not a clinical trial and does not take the place of continuing clinical trials to provide information in support of eventual submission of an NDA.

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 the intended population (e.g., treatment of seriously ill patients without other treatment options versus prophylaxis of low-risk persons likely to have good outcome without treatment).

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 trials 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., depending on the course of a specific emergency situation it may not be possible for a health care professional to provide 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

[24] See the guidance *Emergency Use Authorization of Medical Products* (http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm).

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, and the interim final rule "Exceptions or Alternatives to Labeling Requirements for Products Held by the Strategic National Stockpile" (72 FR 73589, December 28, 2007).

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.[25] We strongly recommend a quality-by-design approach to drug development, as well as the principles described in ICH guidances for industry,[26] although allowances can be made in situations of dire need (e.g., reduced or modified expectation for stability data).

Special CMC considerations may arise for drugs intended for stockpiling. For example, because the distribution of stockpiled drugs during some types of pandemic conditions 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 some types of pandemic situations. 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 studies and humidity variation studies should be carried out to support temperature excursions and humidity changes that are typically encountered during stockpiling.

[25] General guidance pertaining to CMC of drug development can be found on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[26] See the ICH guidances for industry *Q8(R2) Pharmaceutical Development*, *Q10 Pharmaceutical Quality System*, and *Q9 Quality Risk Management*.

REFERENCES[27]

Guidances relevant to general safety and efficacy determinations

Draft guidance for industry *Non-Inferiority Clinical Trials*[28]

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

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)[29]

Guidance for industry *Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines* (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm)

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[27] These guidances can be found on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm unless otherwise noted.

[28] When final, this guidance will represent the FDA's current thinking on this topic.

[29] 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/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm109356.htm).

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

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/MedicalDevices/DeviceRegulationandGuidance/default.htm)[30]

Guidance for industry and FDA Staff *In Vitro Diagnostic 2009 H1N1 Tests for Use in the 2009 H1N1 Emergency*
(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm)

Guidance for industry and FDA staff *In Vitro Diagnostic Devices to Detect Influenza A Viruses: Labeling and Regulatory Path*
(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm)

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/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078583.htm)

Guidance relevant to virologic assessments

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/RegulatoryInformation/Guidances/ucm125127.htm)

Guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review*

[30] When final, this guidance will represent the FDA's current thinking on this topic.