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May 21, 2009

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on Docket ID Number FDA-2009-D-0044 (draft Guidance for Industry: Influenza: Developing Drugs for Treatment and/or Prophylaxis)

Dear Sir or Madam:

The Infectious Diseases Society of America (IDSA) appreciates the opportunity to comment on the U.S. Food and Drug Administration's (FDA) draft Guidance for Industry on Influenza: Developing Drugs for Treatment and/or Prophylaxis" (Draft Guidance). IDSA represents more than 8,500 infectious disease physicians and scientists devoted to patient care, education, research and public health. A number of our members are involved in the pre-clinical development or clinical testing of anti-influenza agents. Seasonal influenza, the threat of pandemic influenza and in particular the ongoing spread of the H5N1 virus and the novel 2009 Influenza A H1N1 ("swine-origin influenza virus") strains are of great concern to the Society.

IDSA applauds FDA for issuing the Draft Guidance. The document is a critical step forward in the nation's preparedness for both seasonal and pandemic influenza efforts, especially at a time when novel influenza strains are rapidly emerging and resistance to currently available antiviral drugs is increasing in prevalence. The rapid development and production of influenza drugs will be essential to the ultimate goal of protecting human health during the annual influenza season or in times of an influenza pandemic.

We strongly support those aspects of the Draft Guidance that seek to clarify the process for influenza drug development, thereby accelerating the availability of treatment and/or prophylaxis for the public good. However, we also have several concerns which are addressed below.

- 1) For severe influenza, the Draft Guidance suggests using either dose-ranging or superiority trials to test efficacy of a drug in hospitalized patients. We are unaware of examples of a dose-ranging trial in Phase 3 development of an antiviral drug that has shown clear statistical superiority. A pivotal study of oseltamivir in uncomplicated influenza of ambulatory adults included two doses, and no differences were observed. No adequately powered trial has been completed for patients hospitalized with influenza, but a high quality case control study suggested that oseltamivir is reasonably effective in treating severe seasonal influenza (McGeer 2007), and retrospective analysis indicates that oseltamivir reduces mortality in avian H5N1 pneumonia despite delays in time to

initiating treatment (Writing Committee NEJM 2008). Therefore, it is unlikely that an effective new antiviral agent would be able to demonstrate superiority compared to oseltamivir. While a superiority study could be reasonably conducted in patients infected with viruses resistant to currently available antiviral agents, the number of such patients is likely to be small, and the ethics of such a trial are challenging. When virus would be susceptible to available agents like oseltamivir, the projected sample sizes for a clinical endpoint would make such designs impractical to conduct.

- 2) For severe influenza, the Draft Guidance states that noninferiority (NI) studies are not possible, because there are no randomized studies that show efficacy of currently effective antiviral drugs. However, the preponderance of evidence suggests efficacy in severe disease and guidelines from the Centers for Disease Control and Prevention (CDC) (Fiore 2008) and IDSA (Harper 2009) recommend treatment with neuraminidase inhibitors for patients with severe disease. Neuraminidase inhibitors (NAI), specifically oseltamivir, also have been recommended for the treatment of severe novel A (H1N1) virus illness by CDC (website) and the World Health Organizations (WHO) (Wk Epidemiol Record 22 May 09). Therefore, placebo-controlled trials are not feasible and of questionable ethics as equipoise does not really exist. We urge FDA to work with companies, the National Institute of Allergy and Infectious Diseases and other federal agencies to define and validate surrogate endpoints, such as viral load quantification, and attempt to relate these endpoints to clinical outcomes. In this regard, an analysis of data from hospitalized adults in Hong Kong (Lee. JID 2009, in press) shows statistically significant relationships between upper respiratory viral loads on admission inversely with time to presentation and directly with co-morbidities. This study also demonstrates significant relationships between time to oseltamivir treatment and reductions in viral loads over time in hospital. An earlier study by this same group reported that oseltamivir treatment in hospitalized adults was associated with reduced duration of hospitalization (Lee Antiviral Therapy 2007). Consequently, the historically controlled data may serve as the basis for justification of NI studies using virologic endpoints, when the data are sufficiently robust. At least one trial of the intravenous NAI peramivir recently has been completed; analysis of initial viral loads (RNA levels and infectious virus titers) and changes over time with respect to clinical endpoints would help to support this conclusion. We suggest that the body of evidence for placebo-controlled trials of neuraminidase inhibitors in ambulatory adults and children is robust and another source of data. Multiple potential endpoints were included and small numbers of high risk patients and persons with severe disease were included in each study. Pooled analysis could provide additional evidence of optimal endpoints and of efficacy in severe disease. Such analysis could be used to develop a rational NI margin. In this regard, clinical endpoints that capture later events reflecting recovery from illness (e.g., time to return to usual functional status) are much more clinically relevant than early events like fever resolution.
- 3) The Draft Guidance adheres to Pediatric Research Equity Act requirements suggesting that separate well-controlled studies with clinical efficacy endpoints and complete safety evaluations must be conducted for the pediatric population.¹ However, considering regulatory, pharmacokinetic and safety hurdles, there may be little incentive to accelerate pediatric drug development. At the same time, longer viral shedding, immunologic naiveté, higher rates of hospitalization, intensive care unit transfers and complications make the pediatric population both a group in great need of therapy and one in which the efficacy of a drug could be rapidly demonstrated. For these reasons and knowing that the study designs

for adult and pediatric populations will differ, sponsors may be dissuaded from developing antivirals for influenza. Therefore, to spur influenza drug development, IDSA urges FDA to encourage sponsors to conduct trials for both study populations in parallel with each other. Additional incentives for timely studies in children are needed.

Finally, from a public health standpoint, antiviral drugs should be easy to use and broadly accessible. Preferred features include simplicity of formulation (oral), simplicity of regimen (low dosing, monotherapy), breadth of efficacy and low-threshold storage requirements. In addition, intravenous formulations are needed for severe disease in those hospitalized with pneumonia and, in some instances like H5N1, possible extrapulmonary involvement. The FDA and other federal agencies should work to find ways to encourage development of drugs with desirable features.

Again, IDSA appreciates the opportunity to provide comments on the Draft Guidance. We trust the FDA will strongly consider our recommendations and would be happy to meet with you to discuss our concerns in greater detail. Should FDA representatives have questions about IDSA's comments, please contact Padma Natarajan, MPH, MS, IDSA's program officer for science and research, at 703-299-1216, or pnatarajan@idsociety.org.

Sincerely,

A handwritten signature in cursive script that reads "Anne A. Gershon".

Anne A. Gershon, MD, FIDSA
President

¹ Pediatric Research Equity Act (Public Law 108-155)