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IDSociety Headquarters
1300 Wilson Boulevard
Suite 300
Arlington, VA 22209
TEL: (703) 299-0200
FAX: (703) 299-0204
EMAIL ADDRESS:
info@idsociety.org
WEBSITE:
www.idsociety.org

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[By Electronic Submission to www.regulations.gov]

Robbin Weyant, PhD
Director, Division of Select Agents and Toxins
Centers for Disease Control and Prevention
1600 Clifton Road, NE; Mailstop A-46
Atlanta, Georgia 30333

Re: CDC-2012-0010: Influenza Viruses Containing the Hemagglutinin from the Goose/Guangdong/1/96 Lineage

The Infectious Diseases Society of America (IDSociety) is pleased to have this opportunity to comment on the request for information referenced above and issued by the Centers for Disease Control and Prevention (CDC) within the Department of Health and Human Services (HHS). IDSociety represents nearly 10,000 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. In considering the issues raised by HHS, IDSociety prioritizes the public's health and welfare. The Society advocates balancing the public health risk of impeding the conduct of H5N1 research against the public health risk of an accidental laboratory release or act of bioterrorism.

In evaluating whether highly pathogenic avian influenza (HPAI) H5N1 viruses pose a severe threat to public health and safety (Questions 1-3), it is important to consider several criteria, including 1) the ability of the strain to be transmitted from person-to-person, 2) the characteristics of the strain in question, compared to naturally circulating strains, and 3) the availability of medical countermeasures (i.e., drugs, vaccines and diagnostics) to mitigate the risk of disease. Circulating HPAI H5N1 influenza viruses containing the hemagglutinin (HA) from the Goose/Guangdong/1/96 lineage do not currently pose a severe threat to public health and safety because they are not readily transmitted between humans. However, H5N1 strains with increased mammalian transmissibility do pose a severe threat to public health and safety, and it is crucial that extensive biosafety and biosecurity measures be taken to prevent accidental release or an act of bioterrorism. This applies to mammalian transmissible H5N1 strains created prior to the current proposed regulation, and to future gain-of-function experiments designed to generate such strains (e.g., deliberate manipulation, reassortment with human viruses). It is just as vital to remember that the benefit-risk calculus is dynamic and should be re-evaluated with changing circumstances and new information. For example, if a mammalian transmissible H5N1 strain were to arise naturally in the wild, it would be critical that some pre-agreed restrictions on research be rapidly lifted to facilitate the urgent development of medical countermeasures to the new strain. If a

mammalian transmissible H5N1 strain were to become the dominant circulating strain in animals or were to show human-to-human transmissibility beyond that observed for current H5N1 strains (e.g., to non-blood-related household contacts, healthcare workers), then immediate steps would need to be taken to facilitate development of countermeasures.

IDSA recommends that HPAI H5N1 influenza viruses containing the HA from the Goose/Guangdong/1/96 lineage viruses be regulated as select agents by HHS (Question 4). H5N1 viruses are currently regulated as select agents by the U.S. Department of Agriculture (USDA) with a focus on agricultural animal health. The involvement of HHS in H5N1 select agent regulation will ensure that the impact on human health is considered when agents are being reviewed. While the intent of the select agent regulation is to regulate HPAI strains, attenuated H5N1 strains that are used in vaccine research are considered select agents until exempted by USDA. The current USDA review process for exemption is often lengthy, negatively impacting public health. If H5N1 is designated as an HHS select agent, the Society urges HHS to speed the appropriate exemption of vaccine strains, and urges HHS and USDA to coordinate efforts in order to prevent additional delays in review.

Beyond the designation of HPAI H5N1 influenza viruses as HHS select agents, IDSA recommends additional consideration of biosafety and biosecurity concerns, depending on the characteristics of the strains in question (Question 7). We envision three categories of HPAI H5N1 virus strains that would be subject to different safety and containment measures. One category includes all strains that arise naturally in the wild. The second encompasses laboratory-derived strains that have been engineered to be attenuated, such as vaccine seed strains with the HA polybasic cleavage site removed and the HA and NA genes incorporated into a virus with backbone genes from low virulence, non-avian strains. Accidental release of these two categories of viruses would pose minimal additional public health risk, as the viruses already exist in the wild or are explicitly weakened. The ability to study these H5N1 strains under currently specified conditions (e.g., BSL2 for deliberately attenuated strains and BSL3 or BSL3-enhanced for circulating HPAI strains) is critical to surveillance efforts and to the development of countermeasures, with clear public health benefits. Furthermore, we recommend that these two categories of H5N1 strains not be subject to Tier 1 select agent designation (Question 5) because the additional security and personnel monitoring would obstruct public health goals.

In contrast, the third category includes strains that have been engineered for increased pathogenicity or mammalian transmissibility without measures to alleviate risk such as those described above. These clearly pose a risk to the public if released. While there can be public health benefit to conducting this work, there is a real possibility of unintentional release of these viruses from some BSL3-enhanced labs that do not meet rigorous standards^{1,2}, with potentially catastrophic consequences. IDSA recommends that HHS consider more extensive biosafety and

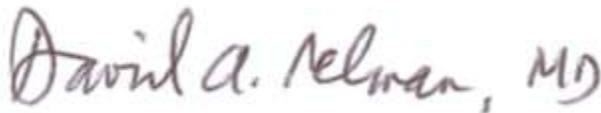
¹ Klotz LC, Sylvester EJ. 2012. The unacceptable risks of a man-made pandemic. Bull. At. Sci. 2012. <http://www.thebulletin.org/web-edition/features/the-unacceptable-risks-of-man-made-pandemic>

² Lipkin WI. 2012. Biocontainment in gain-of-function infectious disease research. mBio 3(5):e00290-12. doi:10.1128/mBio.00290-12

biosecurity measures for work with these strains, above and beyond those measures that are currently required. Details of the new measures should be developed in further consultation with stakeholders. There is a clear need for a framework that will minimize the risk to the public of unintentional release, while allowing important pathogenesis research to be conducted by qualified investigators. For example, HHS could specify that work with such H5N1 viruses only occur in designated BSL3-enhanced labs that have met additional specific training and other requirements. HHS could also monitor the designated labs for the presence of risk-mitigation strategies, such as antiviral stocks, quarantine protocols, etc. Additionally, those working with H5N1 influenza virus with potentially increased mammalian transmissibility (whether naturally occurring or laboratory-derived) should receive H5N1 vaccine when vaccine becomes available. Immunity among laboratory workers can decrease their risk of acquiring infection and likely would decrease the chance of secondary transmission, and is a reasonable prerequisite to working with these viruses. Finally, IDSA recommends that this third category of H5N1 viruses, engineered for increased pathogenicity or mammalian transmissibility, be designated as Tier 1 select agents (Question 5).

IDSA appreciates the opportunity to comment on HHS' proposed designation of HPAI H5N1 viruses as select agents. Should you have any questions about these comments, please contact Audrey Jackson, PhD, IDSA's senior program officer for science and research, at ajackson@idsociety.org or 703-299-1216.

Sincerely,

A handwritten signature in dark ink that reads "David A. Relman, MD". The signature is written in a cursive, slightly slanted style.

David A. Relman, MD, FIDSA
President