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Infectious Diseases Society of America

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[Submitted electronically to nsabb@od.nih.gov]

Samuel L. Stanley, MD
Chairman of the NSABB
Office of Science Policy
National Institutes of Health

IDSA Recommendations to the NSABB to consider during the Risk Benefit Assessment Process of Gain-of-function Research

Dear Dr. Stanley,

The Infectious Diseases Society of America (IDSA) is pleased to offer recommendations to the National Science Advisory Board for Biosecurity (NSABB) as it works with Gryphon Scientific to assess the risk and benefits of gain-of-function (GOF) research on pathogens with pandemic potential.

Ongoing technological advances in the life sciences increasingly offer critical new capabilities for understanding and managing human-microbe interactions. The goals of these efforts include health promotion and disease prevention. At the same time, these same capabilities, especially the means of manipulating genomes and, therefore, the properties of bacteria, viruses, and other infectious agents, pose important risks. Efforts to study and/or predict the natural evolution and emergence of pathogenic microbes by deliberately creating pathogens in the laboratory with enhanced disease-causing and transmission-promoting properties pose the greatest concern. Examples of this gain of function research include the recent creation of highly pathogenic avian influenza viruses with altered host range, enhanced transmissibility, and/or the ability to evade certain forms of human immunity.

ID specialists will be among the physicians who will respond to care for affected individuals in any microbial disease outbreak, be it of natural or human origin—either accidental or deliberate. ID specialists are also among those leading research efforts to counter these disease threats. Accordingly, ID specialists are especially well-positioned to understand the risks and benefits posed by potentially dangerous experiments involving pathogenic microbes and can be valuable advisors for those who will need to undertake complicated risk-benefit analyses (RBA).

IDSA applauds the NSABB for its recent efforts to develop a framework to guide the assessment of risk and benefit of GOF research. The framework highlights key considerations on how to structure this assessment, addresses and evaluates possible alternative approaches, includes the issue of human error or malevolent action, and finally considers the effectiveness of medical countermeasures. We are happy to see

that Gryphon Scientific's risk benefit approach significantly improves on the specificity of the framework, addressing several of our concerns with the draft framework. We offer below six additional points for NSABB and Gryphon Scientific to consider as you work together to assess the risk and benefit of GOF research and develop final recommendations to the U.S. Government (USG).

1. Focus on the GOF experiments of special concern

IDSA remains concerned that the NSABB framework's broad definition of GOF may inadvertently capture areas of research that pose a lower risk to the public. For example, while the NSABB recognizes the benefit of research aiding the development or selection of new or more effective vaccines, its framework still targets influenza vaccine production methods that rely on adaptation of viruses for growth in culture as GOF research. The adaptation and manipulation of wild type influenza virus for growth in eggs or mammalian cell lines are critical to vaccine manufacturing. This approach to produce high growth vaccine candidates has been practiced since the 1940s, and is essential to protect the public from both seasonal and pandemic influenza.

IDSA strongly urges the NSABB to narrow its definition of GOF research to be considered for RBA to avoid this inadvertent capture of low risk research, which is not mentioned in the original White House description of the types of research that should be included in the deliberative process. We recommend that the RBA process focus on research that is reasonably anticipated to result in a pathogen that combines high transmissibility with high pathogenicity in humans, as this combination poses the greatest risk to public health. Such research may involve enhancing either of these properties in a pathogen already possessing the other, or the simultaneous enhancement of both. Whereas other types of GOF research are of concern as well, notably that which increases resistance to known medical countermeasures, they are secondary to the above characteristics. IDSA believes that this definition strikes a balance between impeding experiments with lower risk that society has accepted for many years while ensuring that experiments of special concern are assessed appropriately.

2. Address the uncertainty in estimating both risk and benefit

The risk assessment process provided by Gryphon Scientific will have to use estimated data in the models, as it will have to make assumptions on risks and benefits. Although IDSA understands assumptions are necessary to assess risk and benefit, our society is concerned that Gryphon Scientific has not adequately addressed the uncertainty of its models. IDSA urges the NSABB and Gryphon Scientific to hold robust discussions with experts surrounding the uncertainty of its estimates of risk. We also recommend the NSABB and Gryphon Scientific ensure that its analysis of uncertainty not only include uncertainties in the outcome of the research, such as the pathogenicity changes in a GOF organism, but also the uncertainties in the assessments of likelihood of misuse of the science as well as the consequences of accidents, misuse, and regulations on the conduct of the science. Whereas Gryphon Scientific will use a qualitative assessment of the benefit of GOF research, we urge that the uncertainties around the benefits of research be explicitly considered. Finally, IDSA recommends Gryphon Scientific consider communicating specific assumptions used in its modeling as well as error due to uncertainty to assist the NSABB and other policy makers in better understanding the risk/benefit estimates.

3. Seek a wide breadth of expertise to aid in the RBA process

Gryphon Scientific has indicated that it will interview subject matter experts to obtain additional input to aid its RBA efforts. IDSA strongly supports these actions, and also urges the NSABB and Gryphon Scientific to consider seeking additional perspectives to inform the RBA process, including those of a range of experts in vaccine development, microbial risk assessment, public health response, physicians whose work is primarily clinical, as well as through engagement of the public. In addition, the moral and ethical implications surrounding GOF research have not been adequately addressed in the NSABB framework. Several experts in this field are actively engaged in the GOF debate, and their unique viewpoints can be valuable to the RBA process.

Some stakeholders have expressed concern that the experts best positioned to evaluate the risk and benefits of GOF research are in some cases the ones who are actively conducting the research. IDSA agrees this is an issue that should be considered, and strongly believes that while this RBA evaluation needs as many expert perspectives as possible, they must be transparent with all relevant interests disclosed.

4. Risk should account for the impact on the public perception of science.

One important type of risk that is not included in the NSABB framework, or by Gryphon Scientific's mandate, is the ethical, reputational, and credibility risk for science with the public. The recent laboratory mishaps at the nation's most prestigious laboratories have placed strain on the public's trust for scientific research. Should a USG funded GOF study result in an accident or a deliberate act that places the public at risk, the credibility of science as a whole may suffer. This, in turn, could lead the public to question the quality of public stewardship of biomedical funding and the reliability of scientific and medical advice on risk. This loss of public trust could significantly impair science's ability to inform evidence-based policy decisions. IDSA recommends that the NSABB consider recruiting additional perspectives, such as those with sociology and ethics expertise, to asses this risk as it develops its final recommendations.

5. Risk should account for the impact of any new GOF framework on the course of science.

The ability of humanity to protect itself against pathogens of pandemic potential rests on a vigorous and healthy scientific enterprise. Some, including IDSA members, have raised the concern that as controversy swirls around GOF types of experiments that these fields could abandon certain types of scientific approaches that are powerful tools of scientific inquiry. Furthermore, the concern has been raised that the best and brightest will avoid these areas of inquiry simply because of the weight of regulation, the uncertainty in planning careers in areas subject to moratoriums and increased scrutiny and the controversial nature of the work. If this happens, humanity will be more vulnerable to future threats. IDSA recommends that the possible risk of regulation to the scientific enterprise and, in particular, to certain fields of inquiry be factored in the overall risk-benefit analysis.

6. Consider recommendations on how to make GOF research safer

In Gryphon Scientific's assessment approach for GOF research benefit, it states that it will evaluate "other GOF experiment types" in addition to alternative approaches. IDSA believes these efforts will yield valuable information that may be useful in developing constructive recommendations on how GOF research may be conducted more safely. For example, at the

December 2014 National Academies of Science discussion on the GOF pause, one researcher presented data on how to engineer high risk influenza strains to only undergo productive infection in experimental animals, posing minimal risk to public health. This search for pragmatic solutions that lower risk of GOF has not been widely discussed in the debate, and IDSA urges that this be a more prominent component in the NSABB's final recommendations.

IDSA is committed to ensuring that the broader scientific and science policy community participates in efforts to appropriately guide gain of function research. To complement the NSABB's efforts, IDSA calls for a continued series of transparent broad discussions on gain-of-function and dual use research of concern among stakeholders, including scientists, healthcare workers, policy-makers, ethicists, and representatives from the public. These discussions include the consideration of risk-benefit methodologies, governance models, the place, if any, of classified research, social responsibilities of scientists and journal editors, increased vigilance of biosafety and security concerns, societal values, and, finally, the discussion should solicit international input.

IDSA thanks NSABB for this opportunity to comment, and looks forward to continuing to work with the U.S. Government and those who advise it to clarify the decision-making process on how and whether to undertake high-risk life science experiments. Should you have any questions or concerns about these comments, please feel free to contact Greg Frank, PhD, IDSA Program Officer for Science and Research Policy, at gfrank@idsociety.org or 703-299-1216.

Sincerely,

Stephen B. Calderwood, MD, FIDSA
IDSA President

About IDSA

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii, Klebsiella pneumoni*ae, and *Pseudomonas aeruginosa*, and, finally, emerging infectious syndromes such as Ebola virus fever, enterovirus D68 infection, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and infections caused by bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.