## Comments from Brent and Relman

Office of Biotechnology Activities
NIH/DHHS

To Whom It May Concern

Thank you for the chance to consider the proposed HHS funding framework for gain-of-function research on H5N1 influenza, and the document, "A path forward: framework for guiding U. S. Department of Health and Human Services funding decisions about highly pathogenic avian influenza H5N1 gain of function research".

For what it is worth, we view this proposed framework as a serious and thought-provoking effort to address a complex issue of importance to scientists and to the larger public. We recognize the importance of timeliness, and are grateful for the opportunity to comment on some of the points raised by the framework and the document.

*1) Concerning the statement on draft Page 2.*

*One of the goals of HPAI H5N1 research is to identify the genetic changes that correlate with transmission or enhanced virulence of these viruses in mammals. This information may contribute to pandemic preparedness efforts. Such research may also enable the development and evaluation of countermeasures, such as vaccines, antivirals, and diagnostics for HPAI H5N1 strains that have the potential to spread among humans. The question that ensues is whether HPAI H5N1 gain-of-function research is needed to achieve these aims, and if so, under what conditions such studies should be conducted*.

Here, by HPAI H5N1 GOF research, we refer to that which starts with wild-type HPAI H5N1 virus and adds new functions to it, related to transmissibility, host range or virulence. The last sentence asks whether HPAI H5N1 gain-of-function (GOF) research is needed to contribute to pandemic preparedness, and to the development of countermeasures.

This sentence seems to presuppose that HPAI H5N1 gain-of-function research *can* achieve these aims. The authors agree that such research might be able to achieve these aims under certain conditions, but have not at this point heard arguments for this that we find establish the point and clarify the conditions under which these goals might be achieved.

We therefore suggest that evaluations conducted under a final framework ask two questions, first, whether HPAI H5N1 research *can* achieve these aims, and, second, if it

can achieve these aims, then ask whether HPAI H5N1 gain-of-function research *is needed* to achieve the aims, or whether other experimental avenues might accomplish the same goals by other means (for example, by working with attenuated strains, etc). Such means would often be simpler, less cumbersome, less costly in time and human effort, and require lower levels of containment.

*2) Concerning the disciplinary backgrounds of the scientists who prepare the final framework and who conduct evaluations of benefits.*

We suggest that discussion and evaluation of possible benefits of the research could best be conducted by a wide circle of scientists, including scientists who do not work on influenza or on infectious disease.

The issues concerning the possible benefits of this research cut across a range of topics including viral evolution, drug discovery, vaccine development, and possible methods for sequencing-based surveillance. These topics are intelligible and accessible to broad sections of the community of biological researchers who do not work on influenza, or even on infectious disease. Given a relatively small amount of explanation, they are intelligible to senior scientists in other disciplines including physics and chemistry. We suggest that scientists who do not work on influenza or infectious disease be included in the groups that evaluate the asserted benefits of this work.

Restated, we suggest that any rigorous discussion of possible benefits of these gain of function experiments should involve a broad cross-section of scientists outside the community of infectious disease researchers.

*3) Concerning the scope of the proposed framework for gain-of-function research for H5N1 influenza.*

Researchers worldwide are pursuing GOF experimentation to study changes in host range and determinants of virulence for most other pathogenic animal viruses. By its nature, this framework document does not address such experimentation.

*4) Concerning Box 1 of the document, and Box 2, Criterion 2.*

***Box 1. Applicability of the proposed framework for guiding HHS funding decisions about HPAI H5N1 gain-of-function research***

*HHS will apply this review framework to proposals that are reasonably anticipated to confer gain-of-function attributes to influenza viruses expressing the virulent form of the hemagglutinin (HA) gene from highly pathogenic H5N1.*

***Box 2, Criterion 2***

*The research does not intend, nor is reasonably anticipated to yield an HPAI H5N1 experimental virus*

*that has increased transmissibility, pathogenicity, or expanded host range, unless there is evidence that such a virus could be produced through a natural evolutionary process in the foreseeable future.*

a) Given the paucity of current knowledge, we suggest that the use of the term "evidence that the virus could be produced" might be replaced by "argument based on existing evidence that such a virus could be produced".

b) There are a number of differences between a virus produced via "natural evolutionary processes" in the wild and a virus of the same sequence produced in a lab. Some of these differences may be significant here. In the wild, such a virus will be mixed in with viruses of related sequences that may not be so pathogenic. Such mixed collections of viral genomes may often reside in relatively remote locations, for example, Siberian duck ponds, or in locations where they are unlikely to be, or only infrequently provided access to humans or pigs, etc. For these reasons, the fact that a pathogenic virus to be generated in the lab might exist or come to exist somewhere in nature does not imply that the same sequence existing in nature would be well positioned to enter the human population and cause epidemics. The ecological and anthropological aspects of such viral entry into the human population are not now well understood. By contrast, a concentrated vial of pure virus in the lab, or a virus remade from the nucleic acid sequence in the published literature and in GenBank Nucleotide, may be better able to enter the human population. The mechanisms by which a virus in the lab or the nucleic sequence of the viral genome on the internet might enter the human population are different from the mechanisms the virus might use to enter the human population from our hypothetical duckpond.

c) Given the above considerations, we suggest that HHS open the clause "*unless there is evidence that such a virus could be produced through a natural evolutionary process in the foreseeable future"* to wider scientific discussion before including it in a permanent framework.

d) We note that some persons (although not the authors) might reasonably postulate a moral distinction, that even if a now-undiscovered lethal virus might exist somewhere in nature, or come to exist in the future, there might be a difference between that existence and the construction of the same lethal virus by deliberate human action in a lab.

e) We suggest a "Catch-22" clause. If a future review committee were to decide that a virus "could be produced by natural evolutionary processes in the foreseeable future", and this review were used as sanction for undertaking the work, then we suggest that researchers who made such viruses in the lab should not then be able to claim that the fact that they succeeded in creating such a virus was a surprising result.

*5) Concerning Box 2 of the document, Criterion 5, "biosecurity risks can be sufficiently mitigated and managed".*

a) The first issue here is whether those risks can even be well *assessed*.

That is, we are not sure how to assess the risks that knowledge of a particular set of point mutations that confers human-to-human transmissibility on a reconstructed influenza virus might be used by malefactors (or by self-styled freedom fighters), somewhere in the world. Nor are we sure how, given necessarily imperfect knowledge, any group of scientists and other experts would go about making such an assessment.

b) The next issue requires a thought experiment.

Suppose that it was possible to evaluate biosecurity risks in the present. For example, suppose the world possessed an omniscient worldwide intelligence agency. Further, suppose that this worldwide intelligence agency, which by definition knows and sees all, never makes mistakes by issuing false negatives. Suppose then that this all-knowing intelligence agency assesses that a proposed line of research carries no present biosecurity risk.

Even then, how might an such an intelligence agency be expected to support evaluation of the biosecurity risks in 2023 that might arise from experiments conducted in 2013? Once generated, information about DNA or RNA sequence mutations conferring increased transmissibility or increase virulence will not be un-created. The knowledge of the sequences of the new viruses will persist, even as political structures change. Even an omniscient and infallible intelligence agency would not know the future.

Finally, even supposing an ability to evaluate biosecurity risks in the present and in the future, we are not confident that there are good existing ways researchers and government might "mitigate and manage" the risk that some present or future actor might seek to use sequence information to remake published viruses and then use those to cause harm. We suggest that this matter merits consideration in a final framework.

*5) Concerning one other aspect of the white paper, Page 5*

*"The Department may recommend that certain HPAI H5N1 gain-of-function research is not appropriate for HHS funding because the associated risks cannot be adequately managed if the research were conducted and communicated openly. However, research that is deemed unacceptable for HHS funding, yet is determined to have high scientific and public health merit, could be referred to another department for possible funding under classified conditions."*

We are sensible of the increased scientific knowledge that has come from, and will continue to come from, gain-of-function research that studies viral transmissibility and virulence. As already mentioned, we are less convinced that such research will necessarily lead to better public health preparedness or better countermeasures,

especially in the short-term. For this reason, and given that the results of much gain-of-function work, even carried out under classified conditions, could also be used to cause harm, we suggest that the balance of possible harms and benefits will rarely, if ever, justify classified work of this type.

Sincerely,

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