Written comments for NSABB meeting Jan 7-8, 2016

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Contains original written comments submitted December 31, 2015 plus additional comments (on benefits) submitted January 3, 2016. Additional comments added to this version concern the Benefit Assessment and are in dark red font.

Dear Chairman Stanley and Members of the NSABB:

I am pleased to have the opportunity to offer written comments pertinent to the upcoming meeting of the Board, specifically concerning the Risk-Benefit Assessment provided by Gryphon Scientific and the Working Paper Draft dated December 23, 2015 by the NSABB in response to the RBA. I consider these in order and conclude with some comments on the process. My comments are in no sense a complete evaluation of any of these documents, given their enormous length and the short time available. I may choose to submit additional comments at a later date. These are simply my comments on the most important issues I have noticed in the time available.

In these comments I make reference to written comments submitted by other members of the public. I will not reiterate the details of their arguments, but I register my agreement with them in particular cases.

I. Comments on the NSABB working paper (WP)

Comment I.1. Overall, the working paper accurately identifies that the research involving a reasonably anticipated creation of a strain combining high virulence and high transmissibility is the central "Gain of Function of concern" research that should be the focus of scrutiny. That has been apparent since the start of this process, and it was the NSABB that broadened the charge of Gryphon to include many less-risky experiments. The NSABB has now appropriately narrowed the focus to GOF of concern.

Comment I.2. The scope of GOF of concern identified by the NSABB, however, is unduly narrow. It includes as a condition for GOFoc, not only combined virulence and transmissibility, but also the ability to evade countermeasures. This is inappropriate because countermeasure availability for a transmissible, virulent strain produced by GOF is not guaranteed even to the US, and timely countermeasures will be unavailable for the vast majority of the world. Thus even a strain susceptible to antivirals and to immunity produced by a hypothetical vaccine could do tremendous damage. **Resistance to countermeasures should be deleted from the requirements for GoFoc.**

Comment I.3. The WP fundamentally fails to answer the question posed in the NSABB's own Principle 9 to determine "whether there are certain studies that should not be conducted under any circumstances, and if so, articulate the critical characteristics of such studies." Instead, it states "There are life sciences research studies that should not be conducted on ethical or public health grounds if the potential risks associated with the study are not justified by the potential benefits" (p. 4). **This is an abdication of responsibility given that the Working Paper is a response to a 1000-page RBA.**

Comment I.4. Given the findings of the RBA, the most important of which is that a single year of BSL3 work on mammalian-transmissible high-path avian influenza has an expected fatality toll of some 50+ lives, **creating mammalian-transmissible avian influenza is GOF of the highest concern and should not be undertaken**. Similarly, creation of novel coronaviruses with transmissibility similar to SARS have, by Gryphon's reasoning, an expected toll of >10 lives per laboratory-year. This also is research that should not be

undertaken, by Gryphon's own reasoning (here I rely heavily on the Public Comments submitted by Lynn Klotz). As noted by Klotz, no Institutional Review Board would approve a research plan with an expected fatality toll in this range. The fact that the expected fatality toll is in this case a low probability of a catastrophic death toll should, if anything, be an even stronger bar to such activities.

Comment I.5. Recommendation 2, that "In general, oversight mechanisms for GOF studies of concern should be incorporated into existing policy frameworks" should be modified or replaced. **There is strong evidence that existing policy frameworks are *inadequate* to regulate GOF of concern.** That evidence includes the following:

- Prior to the Funding Pause in October 2014, HHS had put in place a Framework for review of H5N1 GOF research [1] and later for H7N9 GOF research[2]. These frameworks were inadequate in that (i) no formal risk or benefit assessment (ie nothing quantitative) was done when HHS considered these studies [this I have heard from a participant in the review]; (ii) the review was done in private with no public input; (iii) the same day that the H7N9 framework was published [2], Fouchier and colleagues published a paper describing HHS-sponsored GOF research on H7N9 (see http://comments.sciencemag.org/content/10.1126/science.1244158). This is prima facie evidence of the inadequacy of the Frameworks.
- During the funding pause, Baric and colleagues published a paper [3] describing NIH-funded experiments that by any standard met the terms of the funding pause: "may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route." While the circumstances surrounding this work (in particular why it was permitted under the funding pause) have not been publicly described, this is clear evidence that even enhanced scrutiny may be circumvented by NIH as funder and/or an investigator.
- These instances, along with common sense, indicate that placing NIH or CDC (both direct funders and in the case of CDC, performers of GOF of concern research) as the judges of what may and may not be performed is a direct conflict of interest and is not a way to arrive at impartial judgments.

Given these considerations, an interagency task force that receives input from HHS but is independent of it seems much preferable to existing mechanisms[4]. Expansion of the Select Agent rule to prohibit GOF of concern without the specific consent of such a board would be a possible policy solution.

Comment I.6. **The suggestion to use existing regulatory approaches for regulating GOF of concern requires that institutional oversight have the capacity to deal with this topic, making fine distinctions that have not yet been defined, much less codified in ways that can be applied at the institutional level.** There is no reason to think that Institutional Biosafety Committees have the requisite expertise to perform risk-benefit evaluations on this scale. As an example, the minutes of the University of Wisconsin IBC obtained by *Nature* for GOF work by Prof. Kawaoka (http://www.nature.com/polopoly_fs/7.18249!/file/WISC_Review.pdf) contain no numerical estimates of risk (that is to say, do not perform risk assessment, although they assert on p. 1 that it includes a risk benefit assessment) and accept uncritically all assertions of the investigator about benefits of the proposed work, including false statements ("The proposed research will determine the likelihood of an influenza virus similar to the 1918 pandemic strain of [sic] emerging naturally." The research has been published, and that likelihood has not been determined. Thus the benefit assessment cannot be considered adequate either. *This further demonstrates the inadequacy of existing regulatory mechanisms to deal with GOF of concern.*

II. Comments on the Gryphon Risk-Benefit Assessment (RBA)

Comments on Biosafety Risk.

Comment II.1. There is a presumption in the RBA, starting with the Executive Summary, that experiments with the pandemic H1N1 strain of 1918 constitute an acceptable level of risk against which other experiments should be compared. Moreover, it is stated (section 1.1) that " No GoF experiment is likely to create a strain riskier than work with wild-type 1918 H1N1." **Both the assumption that this level of risk is acceptable, and the claim that no GOF experiment is likely to create a strain riskier than work with wt 1918 H1N1, are unjustified.** The source of either claim is unclear, and in particular the claim that no more dangerous strain exists is based on a misreading of the literature on H1N1 case-fatality risk (see comment below). The quoted statement also directly contradicts the statement (RBA p. 78-9): "In short, a strain of influenza virus that is as transmissible (or to which the population has as little minimal immunity) as newly emerged pandemic strains WHILE leading to a case fatality rate of more than 5%, would pose more of a risk of a global pandemic than any wild type strain heretofore identified. No experiments that are likely to be conducted under the rubric of GoF research will drive risk more than this combination of traits or significantly increase the risk of a laboratory acquired infection."

Comment II.2. The RBA appropriately identifies creation of novel viruses combining mammalian virulence with mammalian transmissibility as the most risk-enhancing experiments (Figure 6.1). Notably, it does *not* add "resistance to countermeasures" to this category, although it does note that resistance to countermeasures would further enhance the risk of such experiments in the developed world, where countermeasures might be available. **I recommend that the NSABB adhere to this classification, without requiring resistance to countermeasures, when defining GOF of concern.**

Comment II.3. Notwithstanding the serious flaws in the analysis that lead to an underestimate of the risk of such experiments, I draw the NSABB's attention to the fact that: Using Gryphon's own numbers, the expected fatality toll from a lab-year of coronavirus experimentation with enhanced transmissibility in BSL3 is approximately 16 fatalities

(Written comments of Lynn Klotz to the NSABB, December 2015). A corresponding calculation for mammalian-transmissible avian influenza would be around 50 fatalities. **Absent an exceptionally compelling prospect of life-saving, justly distributed benefits, this conclusion from the RBA merits the immediate discontinuation of experiments meeting the definition of GOF of Concern proposed by the NSABB, with the modification suggested above to remove the requirement for escaping countermeasures.**

Comment II.4. The RBA contains a number of erroneous parameter assumptions that lower the estimate of risk of various experiments relative to appropriate estimates. These are shown in a table below.

Table 1: Errors in the Risk Assessment Leading to Underestimate of Risk

Assumption	Source of Error and corrected assumption	Impact on risk estimates
CFR of 1918 influenza is 10-20% of infected persons (Table S7 in supplement http://www.gryphonscientific.com/wp-content/uploads/2015/12/Supplemental-info-disease-course-of-influenza.pdf)	Misreading of a graph in the reference cited, ref 82. Actual values are mainly in the range of 0.5%-3% of those with clinical disease (except for extremes of age). This is therefore a 6-20x overestimate, not accounting for medical improvements and larger denominator of asymptomatic cases)	Allegedly acceptable risk of experiments with 1918 pandemic flu are significantly overstated, raising the bar for what should be permitted to a much higher level and seemingly justifying false statements like that noted in Comment II.1.
CFR of influenza is 0.0001%-0.00043% of those infected (Table S7 in supplement http://www.gryphonscientific.com/wp-content/uploads/2015/12/Supplemental-info-disease-course-of-influenza.pdf)	Error source unclear. Actual estimate from authoritative systematic review [5] is 0.001%-0.010%. Thus this is more than a 10x error.	Suggests manipulations of seasonal influenza have smaller risk than they do.
R0 of SARS is 1.5, may go as low as <1 (http://www.gryphonscientific.com/wp-content/uploads/2015/12/Supplemental-information-R0-of-CoV.pdf).	This seems to result from a combination of not understanding what R0 is (it does not incorporate the later stages of the epidemic or the impact of control measures), especially as used in a branching process. Averaging over different phases of the epidemic is completely inappropriate. Two of the three authoritative estimates of R0 are not cited; with Riley (cited) they all estimated approximately 3.0 [6-8]	Significantly underestimates severity of SARS outbreaks
Control measures (community mitigation) will be effective	There is no evidence of this in modern influenza pandemics	Underestimates severity and probability of pandemic from

		modified influenza strains
Assumes that all event trees for LAI happen in the source lab at the specified biosecurity level	Errors with a probability of leading to a LAI have repeatedly, consistently occurred outside the source lab, usually at a lower BSL. For example, 2014 CDC anthrax exposure occurred in BSL2 after inadequate decontamination; 2014 CDC HPAI exposure occurred outside source lab (though fortunately at BSL3) due to contamination of sample; 2014 CDC Ebola exposure occurred at BSL2 due to falsely assumed decontamination and removal to lower BSL; 2015 DOD anthrax exposures occurred in conditions designed for inactivated anthrax because of lack of proper inactivation.	This leads to neglect of a fault tree that routinely occurs in top US government labs, in which the probability of LAI is higher, the likelihood of its going undetected is higher, the likelihood of having prophylactic measures in place for laboratorians is lower, and thus the risk of outbreak and escaping local control is higher. For more details, see [9].
Probability that a single LAI with a pandemic-capable influenza triggers a pandemic is 0.4%.	Other branching process models, which account for negative-binomial overdispersion, find estimates of 5-60%[6, 10, 11]	Vastly underestimates by 1-2 orders of magnitude all risks.

Comments on biosecurity

These may be supplied at a later date when time allows.

Comments on benefits of GOF

Comment II. 5. A very good feature of the BA is the consideration of alternatives to GOF experiments to either answer the same scientific questions or achieve similar public health benefits in a different way. Had appropriate skepticism been applied to the claims of those performing and sponsoring GOF research, these alternatives would have proven far more

compelling than the Benefit Assessment suggests**. The extreme skew of the experts consulted for the Benefit Assessment (see Section III below), combined with a surprisingly credulous evaluation of their claims, leaves the BA with a number of statements that do not stand up to scrutiny.**

Comment II.6. The vast majority of the public health benefits asserted for GOF experiments are for the development of costly countermeasures, including vaccines and antiviral drugs**. These benefits will be limited to the wealthiest populations, which have access to the newest drugs and vaccines.** This problem is recognized in the BA, for example with respect to antiviral development in the statement (p. 438): "In sum, although U.S. policy supports the donation of influenza antivirals in the event of a pandemic, the relatively small number of doses donated in comparison to the global need in the event of a pandemic means that developing countries would face shortages, which would in turn exacerbate poor usage in-country." In the case of pandemic preparedness benefits, similar statements are made (pp. 442 and 444) In contrast, the risks of GOF research, which are distributed globally and if anything will fall harder on lower-resource populations, [12], As recently as 2009, developing countries had little access to antivirals or vaccines until long after the peak of pandemic risk. **In this sense, GOF experiments unjustly require unconsenting populations to bear pandemic risk while promising them no realistic prospect of benefit. This is a serious and independent ethical objection to such research, which is not adequately addressed in the separated ethical analysis commissioned by NSABB.**

Comment II.7. At multiple points in the BA and in the corresponding section of the Executive Summary (1.4), there are statements that particular types of experiments involving the evasion of novel therapeutics or vaccines involve no human health risk because the countermeasures are not yet extant. This statement is false unless one assumes that the immunity produced by novel vaccines, and the protection by novel treatments, is unrelated to that produced by existing natural exposure or vaccines (for immunity) or antivirals (for resistance). Vaccine-related immunity and natural immunity may involve the same epitopes (especially as vaccine development is often based on observations of naturally acquired immunity), and cross-resistance between novel and existing antivirals within a class is expected, just as cross-resistance within existing classes (eg zanamavir and oseltamivir, or

rimantadine and amantadine) can occur with the same mutation. **In summary, these statements -- that GOF to evade countermeasures not yet available has no human health risk -- are unjustified and tend to underestimate the risk of corresponding GOF experiments.**

Comment II.8. Virtually all of the benefits of GOF experiments described in the Benefit Assessment are characterized as *not* unique to GOF (Table 9.1, 3rd column). This is extremely important, as it means that the Benefit Assessment characterizes nearly all of the claimed benefits as being achievable by alternative means. While some of these alternative means involve localized risk of infection of a few laboratory personnel, these risks are minimal in comparison to pandemic risk. Thus **the BA implies that nearly all of the benefits of GOF (especially of GOF of concern) could be achieved with alternatives that avoid the vast majority of GOF risk. This finding creates a strong presumption in favor of alternative approaches [13]. Indeed, under such circumstances, I would argue it is unethical to perform GOF of concern experiments[14].**

Comment II.9. It is stated (Section 1.4, p. 6) that "GoF approaches that enhance virulence represent the most efficient and effective strategy for discovering novel virulence factors, which may be good targets for new therapeutics." This does not make sense. If the virulence factors found are not present in naturally circulating strains, then finding changes that could result in increased virulence could only facilitate the development of therapeutics for strains that do not exist. **Development of therapeutics for nonexistent strains would be a highly speculative activity with little likelihood of being supported in the absence of a foreseeable market.**

Comment II.10. The most important unique benefit asserted for GOF of concern (enhancement of mammalian transmissibility of avian influenza) is informing pandemic risk assessment and prioritization of countermeasures. The BA asserts these are of particular importance in rapid risk assessment and prioritization: "GoF data play an important role in rapid risk assessments when novel flu viruses first emerge in human populations due to the early availability of sequence data. These risk assessments facilitate more rapid initiation of response activities such as pre-pandemic vaccine development" (p. 244).

The assertion of these unique benefits represents an uncritical acceptance of the assertions of GOF proponents that is contrary to the evidence. The assertion has four **fatal flaws**:

1. **Every mutation cited by GOF proponents as having been discovered in GOF experiments and used to prioritize pandemic response [15, 16] has been found (in most cases prior to the GOF studies) in a non-dangerous, non-GOF study and identified as a predictor of pandemic risk.** Thus the claim of uniqueness is unjustified (see Table below). Alt-GOF can, and indeed have, identified mutations and phenotypes of concern.
2. While it is true that GOF-identified mutations have been used to inform surveillance and preparedness strategies, **there is no evidence that the use of such findings has improved the accuracy of these strategies.** Using information is different from using it productively. There is no case in which a pandemic has been anticipated using GOF-derived data. The evidence that decisions are improved is weakened even further by the fact that many GOF mutations have highly context-dependent effects, so that they may or may not be predictive in actual wildtype strains [17, 18].
3. **GOF data may be misleading, resulting in worse not better decisions.** In the one case when a pandemic has emerged during the era of widespread virus sequencing (2009) it lacked the mutation PB2 E627K[17], which has been identified as perhaps the most important single GOF mutation for mammalian adaptation [19]. Surveillance did not identify this virus in swine before it became pandemic, but had it been identified, use of GOF data would have incorrectly classified it as low risk. Ruling out one of the four strains that caused a pandemic in a century as low risk would be a remarkably large error. Incidentally, this story also highlights the uselessness of any genetic information when surveillance does not catch a strain before it emerges. No pandemic strain has ever been discovered in animals before it caused a pandemic.
4. The accuracy of ferrets in predicting human transmissibility is imperfect, though they are the best available model [20]. Indeed, **several GOF researchers and proponents have said in public meetings that they expect the strains isolated from ferret transmission experiments would not be readily transmissible in**

humans. This uncertainty nullifies or even negates the benefit for pandemic preparedness, because mutations identified in these studies, which are being used as *positive predictors of human pandemic potential*, are in fact uncertain predictors and may not indicate human transmissibility. This could mean that strains with little human pandemic potential are tagged for special prevention efforts, and/or that strains with different genetic profiles that are actually high-risk are identified as low-risk and deprioritized. Notably, this uncertainty makes the use of such mutations highly impractical for decision-making, yet it does not nullify the risk presented by these strains. It negates or nullifies the benefit, and yet only reduces the risk, because the statement that the GOF strains would not be pandemic-capable in humans are informed guesses, which may be wrong.

Table 2: Non-uniqueness of benefits for GOF of concern studies for pandemic response

Mutation claimed to be significant based on GOF by Davis [15]or Schultz-Cherry [16]	Prior studies not involving PPP creation that identified these mutations	Counterexamples
H5 &H7N9 HA Q222L HA	[21-23] [18, 24-26]	CONTEXT DEPENDENCE: Changes do not quantitatively shift receptor binding in related H5 strains [18]
H5N1 HA S133A S135N S123P S155N	[23, 27]	
H7N9 HA T156A, Q222L	[28, 29]	
PB2 E627K, D701N	[30]	MISLEADING INFERENCE: Both absent in 2009pdm [17]. Would have led to its misclassification as low risk

Comment II.11. I endorse the critiques submitted as comments to the NSABB by Dr. Stanley Plotkin of the asserted benefits of GOF experiments. These represent further examples of the widespread exaggeration of benefits and downplaying of alt-GOF in the Benefit Assessment. I will not recapitulate these here but simply incorporate them by reference to his remarks.

III. Comments on the NSABB process

On the whole, I would characterize the process of the RBA development as distinctly unwelcoming of public participation, and as heavily weighted in favor of those who do and fund GOF of concern research. Major shortcomings include the following:

- At all in-person meetings of the NSABB including the upcoming one, public comment has been possible only in writing or in person, but not in real time by any electronic medium. This excludes many persons who may wish to comment in real time on the proceedings but do not have the ability to attend in person.
- The development of the RBA included site visits and conversations with many investigators in 14 labs, most of which do GOF research. The benefit assessment in particular received more than 80 percent of its input from scientists who do PPP research or representatives of agencies that fund it (RBA Fig. 9.3). In contrast, only about 10 (12%) of those interviewed for the benefit assessment were persons who have expressed reservations about RBA research.
- The timeline for public comment was extremely short, with the NSABB waiting apparently 2 weeks from the time it saw Gryphon's RBA until it posted it publicly, and then only 1 month (including Christmas and New Year's) before its meeting. There were only 8 days including Christmas from the release of NSABB's draft working paper to the deadline for public comments to be submitted and seen by the NSABB members.
- The unbalanced representation of GOF researchers/funders versus those who have raised concerns is continued in the agenda for the January 7-8 meeting. 3 outspoken critics are on the panels, plus one additional member of the Cambridge Working Group; 9-10 funders or researchers of GOF studies are speaking. This imbalance was raised in plenty of time to the NSABB leadership, which chose not to address the problem.

Overall, it is difficult to see this process as having been designed to maximize public input or to achieve balance between proponents and critics of GOF, or indeed to address the

inherent conflicts of interest of those whose research or funding portfolios are at issue in the discussion.

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15. Davis, C.T., et al., *Use of Highly Pathogenic Avian Influenza A(H5N1) Gain-Of-Function Studies for Molecular-Based Surveillance and Pandemic Preparedness.* MBio, 2014. **5**(6).

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20. Buhnerkempe, M.G., et al., *Mapping influenza transmission in the ferret model to transmission in humans.* Elife, 2015. **4**.

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