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Additional Interview Data: Research Proliferation, Practical Considerations for GoF Policies, and Limitations of Alternative Approaches

Gryphon Scientific conducted interviews with 86 GoF stakeholders to inform the Risk and Benefit Assessment (RBA) of Gain-of-Function (GoF) research. Interviewed stakeholders include researchers who study influenza viruses and coronaviruses (Pathogens with Pandemic Potential, or PPPs), including graduate students, postdoctoral fellows and senior researchers, and principal investigators; non-PPP researchers, and government and industry representatives. This document summarizes interview data that were not directly incorporated into the RBA but are relevant to the overall deliberative process for developing a new USG GoF research policy and may inform the NSABB's deliberations. The summary is split into four sections: (1) comments related to the current regulatory environment for conducting GoF research (i.e. those policies in place prior to the moratorium); (2) comments related to the effect of the GoF debate on researchers' interests in continuing to pursue GoF research, in particular young investigators; (3) key considerations for the development and implementation of a new GoF research policy; (4) comments related to the use of attenuated virus strains as a risk mitigation strategy. All commentary in this document reflects the opinions of interviewed stakeholders.

Assessment of the Current Regulatory Environment

As noted by the NSABB working group, a large fraction of what constitutes GoF research involving pathogens with pandemic potential (PPPs) is already captured by existing regulations: select agent regulations (SARS-CoV, highly pathogenic avian influenza viruses, the 1918 H1N1 pandemic influenza virus); the HHS Framework for guiding funding decisions about research proposals with the potential for generating mammalian-transmissible HPAI viruses; and BL-3 high-containment laboratory regulations (which cover MERS-CoV, SARS-CoV, and several influenza viruses). **Many PPP researchers felt that the administrative burdens associated with conducting high-containment lab research and select agent research are already extremely high.** Both Principal Investigators (PIs) and Environmental Health and Safety (EH&S) personnel noted that in order to achieve regulatory compliance and ensure that such research is carried out safely and securely, they devote significant amounts of time to developing standard operating protocols (SOPs), training, tracking inventory, writing documentation to receive approvals for experiments from local IBCs or national-level funding agencies, etc. Critically, these tasks cannot be outsourced to research assistants or administrative staff, as all documentation and training exercises must be grounded in practical lab experience. These regulatory burdens are especially demanding for young investigators starting their own labs, when added to the challenges of establishing a new research program and achieving tenure, already extremely difficult and stressful in the current funding environment. For this reason, multiple young investigators currently engaged in select agent and/or high-containment research are not interested in continuing this type of research when starting their

own research programs. In addition, EH&S stakeholders from one institution stated that they would encourage their administration to be cautious in agreeing to host a new high-containment or select agent lab, given the effort needed to achieve regulatory compliance. These stakeholders also stated that they were aware of other institutions that had consciously decided not to pursue select agent work on their campuses due to the high level of administrative effort and funding required. (Gryphon did not interview any university administrators to corroborate this information.) Collectively, stakeholders strongly encouraged decisions about new GoF research policies to consider their experiences in the current regulatory environment.

Effect of GoF Debate on Research Proliferation

When asked whether the current controversy surrounding GoF research and the funding pause influenced their interest in continuing to pursue research involving influenza viruses and coronaviruses, the answers of PPP researchers at all levels were strikingly varied. Some researchers are committed to staying in these fields regardless of the outcome of the deliberative process, given their strong interest in the subject matter (from both scientific and public health perspectives) and their research expertise. **However, many researchers stated that the GoF debate and research pause have significantly lessened their desire to pursue PPP research in the future.** (Of note, these comments reflect researchers' enthusiasm for continuing PPP research in general and are not restricted to GoF research involving influenza viruses or coronaviruses.) Importantly, PPP researchers at all levels – PIs, postdocs, and graduate students – fall into both categories.

Researchers provided multiple reasons for their reluctance to continue PPP research. **One major concern is the uncertainty in whether and how GoF research will be conducted in the future and whether additional research pauses will occur.** Researchers stressed that research pauses are incredibly disruptive to their careers, in particular young investigators who are worried about prolonging their graduate or postdoctoral training. Several PIs reported unwillingness to place their trainees on projects involving GoF approaches, out of concern that future research pauses will delay or compromise trainees' abilities to graduate or secure independent investigator positions. In addition, researchers noted that while large labs with robust funding and diverse research projects are likely to be able to continue operating during a research pause, a research pause could be financially and scientifically devastating to a small lab with a more focused research program. One senior researcher described the threat of closing down labs as a "game changer" for young scientists, and many graduate students and postdocs agreed that they are uncomfortable banking their careers on GoF research in the current science policy climate. Overall, PPP researchers were worried that the outcomes of the current deliberative process would not resolve or reduce this uncertainty and therefore expected this concern to significantly influence their career decisions over the next few years. Young investigators were additionally concerned about their ability to compete for jobs with postdocs in other fields of research. Postdoc interviewees in particular stated their fear that universities would be biased toward choosing candidates in non-controversial fields, regardless of scientific merit, and noted that universities are also hurt by research pauses due to reductions in their overhead money during that time. (Of note, Gryphon did not interview any university administrators or members of faculty hiring committees to corroborate these statements.) Our observations about the negative effects of the GoF debate on young investigators are echoed by the results of an informal poll of

graduate students and postdocs conducted by Dr. Julie Pfeiffer and published in *mBio* in January 2015.[1] Dr. Pfeiffer found that more than one-quarter of respondents reported that they were less likely to work on influenza, SARS-CoV, or MERS-CoV in the future, while only 5% said that they were more likely to work on these pathogens and half said their plans were unchanged. (An additional ~15% said that they were not planning on researching viruses in the future.)

Several additional concerns affected all levels of researchers equally. **Multiple researchers would consider leaving the field of PPP research if the current restrictions on GoF experiments persist because they feel that the quality of their research is significantly compromised under these restrictive conditions.** As detailed in the benefit assessment, across all GoF phenotypes, certain types of scientific studies that rely solely on alternative approaches, in particular mechanistic studies, are less rigorous than studies that also include GoF approaches. The inability to use GoF approaches is not only scientifically frustrating but also may place PPP researchers in the US at a competitive disadvantage for winning grants and publishing papers, relative to their foreign peers and US scientists studying other pathogens. Finally, GoF researchers were frustrated that their work has been taken out of context and demonized in the scientific and popular media. Interviewees noted that many researchers who study PPPs and other infectious diseases have been reluctant to correct popular misconceptions and speak out in support of GoF research, seemingly out of concern that their work could also be affected. GoF researchers generally agreed to the need for better public engagement about their research but thought that the rhetoric of the current debate will make this effort more difficult. Overall, researchers felt that the "undue judgement" of their work has been demoralizing and has heightened their concerns about pursuing PPP research in the future. For all of these reasons, several postdoc interviewees stated that they are strongly considering pursuing PI positions abroad rather than in the US.

This "anti-proliferative" effect of the GoF debate is already apparent at several institutions. Since the GoF controversy ratcheted up in 2012, several institutions have already observed a decrease in the size of their trainee population. One high-containment lab manager explained that the time she dedicates to training researchers in conducting lab work in the BL-3 suite has dropped from 70% to about 5% since 2012, as new researchers are no longer joining the lab. Additionally, several PIs stated that getting and graduating talented graduate students has become more challenging over the past few years. Finally, the concerns detailed above have influenced the private sector as well as academia. One researcher stated that a biotech company he has been collaborating with on therapeutic development has paused all studies that could be perceived as GoF due to public relations concerns, even those types of studies that were granted exemptions from the moratorium following the initial announcement.

Key Considerations for Implementing Policies that May Restrict GoF Research

GoF stakeholders shared several opinions about key considerations for developing a GoF research policy that is reasonable, can be operationalized, and does not preclude the ability of PPP researchers to remain competitive in their fields. The first set of considerations supports the development of a research policy that is not unduly burdensome to investigators and to EH&S personnel who oversee the safe conduct of research on their campuses. Many interviewees advocated for any new research policy to build on existing regulations (e.g. DURC, select agent rules, etc.), in order to minimize administrative burdens.

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[1] Pfeiffer JK (2015) Is the debate and "pause" on experiments that alter pathogens with pandemic potential influencing future plans of graduate students and postdoctoral fellows? *MBio* 6

Interviewees also urged careful consideration of the timing of implementation of any new regulations, in the context of ongoing regulatory changes (such as the establishment of institutional DURC policies). EH&S stakeholders emphasized that it is critical to examine the potential consequences of any new research policy for EH&S personnel, particularly whether additional resources or expertise are needed for their groups to effectively implement the policy. Some EH&S stakeholders feel that their offices are already under-funded and over-worked, and as the regulatory environment becomes more complex, keeping up with changing and expanding regulations becomes increasingly challenging without provision of additional support from the government or their institutions.

The second consideration seeks to avoid unreasonable restrictions on PPP research. **Several researchers advocated for the development of a focused research policy that regulates at the level of individual experiments rather than generalized classes of experiments.** Stakeholders felt that establishing focused and meaningful definitions of general types of GoF research of concern would be extremely difficult, voicing strong concerns that such definitions would inadvertently encompass experiments that are not risky. **Stakeholders also emphasized that any new research policy must clearly define the scope of research subject to the regulation, as the imprecise nature of the current definition of GoF research caused widespread confusion the institutional level.** Several institutions interpreted the definition quite conservatively when deciding which studies to pause; as a result, these institutions likely ended up ceasing to work on certain projects unnecessarily. Without a clearly defined research policy moving forward, such over-interpretation could readily occur again.

The third set of considerations reflects concerns that US influenza and coronavirus researchers will not remain internationally competitive if additional GoF research regulations or restrictions are put in place. These concerns stem from the fact that studies incorporating GoF approaches are often more scientifically rigorous than studies relying solely on alternative experimental approaches. **As mentioned above, PPP researchers voiced concern that an inability to conduct GoF experiments would compromise their capacity to compete for grants, to publish papers, and (for young investigators) to secure principal investigator positions.** With respect to grants, within a given study section, influenza and coronavirus researchers are competing against researchers who study other pathogens for a limited pool of money. When comparing PPP and non-PPP studies solely on the basis of scientific merit, PPP researchers pursuing similar scientific questions with a reduced set of experimental tools may be at a scientific disadvantage relative to non-PPP researchers. With respect to publications, PPP researchers are competing not only against non-PPP researchers but also against foreign PPP researchers who may be working under less restrictive research conditions. Once again, comparing the scientific rigor of domestic PPP studies to that of studies involving other pathogens or conducted abroad may render PPP researchers less likely to publish in high-impact journals or less likely to publish overall. Additionally, several researchers referenced scenarios in which reviewers requested GoF experiments that are currently subject to pause, thereby delaying (or potentially precluding) publication of their work. As reviewers are accustomed to evaluating manuscripts based on scientific merit and providing suggestions without explicitly considering biosafety or biosecurity issues, such requests are likely to occur again in the future. Finally, several PIs expressed reluctance to hire new postdocs because they are worried about providing postdocs with rigorous projects that will position them to be competitive on the job market against non-PPP researchers. Collectively, these concerns are already discouraging young scientists from remaining in the field of PPP research, as detailed above. Consequently, discussions about how to craft and

operationalize a new GoF research policy should consider strategies for mitigating these concerns, such as adjusting the nature and timing of the GoF review process.

Additional Research Needed to Support More Widespread use of Alternative Approaches

Collectively, PPP researchers expressed strong interests in pursuing alternative approaches that pose less risk whenever possible but shared several challenges that practically limit their current use of alt-GoF approaches. This section focuses on alt-GoF approaches that involve using model viruses (e.g. mouse hepatitis virus as a model for MERS-CoV or SARS-CoV) or attenuated viruses (e.g. reassortant viruses with the highly attenuated lab strain PR8) in lieu of the wild type strain. **One key limitation is that, in many cases, the "cost' of using attenuated strains is not well-understood.** That is, researchers do not yet understand whether the attenuated strain serves as a good proxy for the wild type strain, or whether results using the attenuated strain are likely to be generalizable to the wild type strain. This statement holds true across all types of attenuated strains: reassortant strains with attenuated viruses, highly pathogenic avian influenza strains with the HA multibasic cleavage site mutated or deleted, replication incompetent strains, etc. PPP researchers emphasized that additional research is needed to establish whether and when attenuated strains can be used for different types of GoF experiments. **Although this kind of research serves as a critical foundation for expanding the use of attenuated strains in influenza and coronavirus research, securing funding for and publishing this research is extremely difficult because it is not considered ground-breaking. Obtaining funding for and publishing basic biological research using model viruses or attenuated strains is similarly difficult.** If the science policy and research communities would like to see expanded use of model viruses and attenuated strains in the influenza and coronavirus fields as a risk mitigation measure, supporting studies to validate their use and ensuring that reviewers do not penalize grant applications and publications involving model/attenuated viruses is critical.