Thank you for the opportunity to answer these questions. My answers are in italic font directly beneath the question asked.

The Honorable Dr. Michael Burgess

Mr. Pekosz, continuing my interest in your written testimony about closing the loophole, specifically that "biosafety is independent of funding sources

1) Can you expand on your answer and what you believe Congress should do to achieve that goal of independent oversight over biosafety?

Certain biosafety review processes that involved enhanced pathogens and experiments that may increase their disease potential or transmission only apply to NIH-funded grant proposals. Biosafety is independent of funding source so the process of enhanced pathogen review should be applied to specific pathogens and specific types of experiments irrespective of funding source. Congressional actions that expand the NIH review processes already in place to experiments funded by any type of support, at any type of research institute (public, private or government) would increase biosafety tremendously and in a relatively simple way.

The Honorable Morgan Griffith

1) During an experiment done in any biosafety level lab, if there is a progress report that is not reported or is delayed in being reported, what are the current protocols to address this issue?

Progress reports for most NIH funded grants involve the investigator and the institution the investigator works at. They are usually asked for at the end of a funding cycle – usually one year – and involve the investigator summarizing the work done with the funds that were spent and the institution reporting on exactly how much was spent and on what particular items (salary, benefits, laboratory supplies, etc.). Research grants from NIH are technically awarded to institutions, so it's the institution that is responsible for submitting these reports. Since these reports are tied to the end of a fiscal year, the release of funds for the following fiscal year could

be delayed, pending the submission of progress report. So the investigator and institution are responsible for submitting timely and complete progress reports, and the NIH is responsible for approving those reports.

2) Experiments conducted in biosafety level 4, the highest-level containment facilities, are physically demanding on researchers. Researchers typically have to wear full enclosed protective suits that connect to oxygen lines. They can't eat, drink, or go to the bathroom while during the experiment The bulkiness of the protective equipment slows down movement. The upper limit recommended for working in these conditions is 3 hours. BSL-4 lab space is also in high demand, meaning that experiments have to be scheduled months in advance. a. Is there any oversight into research being done in a biosafety level-3+ lab by federal agencies?

Yes, there is a significant amount of federal oversight done on BSL3/BSL3+ laboratories and additional oversight for BSL3 experiments performed in animal models (ABSL3 research) or in arthropod vectors (ABCL3). Much of this is dependent on the specific agent being used. As an example, my laboratory recently had an inspection from the CDC that went over all the protocols and procedures we use to work with SARS-CoV-2. Animal facilities are inspected by other agencies including the USDA. Any NIH research proposal has to address biosafety and animal experiments and ensure that the appropriate, inspected and fully functioning facilities are present for the proposed work.

b. What are the current protocols to decide to perform research in a biosafety level-3+ labs instead of a biosafety level 4 lab?

The starting point for all discussions of biosafety level is the CDC's Biosafety in Microbiological and Biomedical laboratories manual, or the BMBL (https://www.cdc.gov/labs/BMBL.html). That document lays out the basic biosafety and laboratory parameters needed perform specific experiments with specific agents. The investigator wishing to perform this research, then has to obtain Institutional Biosafety Committee (IBC) approval at their institution for the proposed research and level of containment. The IBC takes into account the specific biosafety laboratories

and trained personnel present at the institution before deciding whether to approve a particular set of experiments with a particular agent.

All of these factors incentivize researchers to conduct as much of their experimental work as possible in BSL-2 and BSL-3 facilities. Many research institutes operate what is called BSL-3+ or BSL-3 enhanced laboratories. These are standard BSL-3 facilities that incorporate some but not all of the biosafety and containment measures in BSL-4 labs. However, BSL-3+ is not an official biosafety level and there are no defined standards. Therefore, it is unclear if BSL-3+ facilities have the appropriate level of biosafety measures.

a. Is there any oversight into research being done in a biosafety level-3+ lab by federal agencies?

BSL3+ research is described in the BMBL and the decision on what particular enhancements are added to BSL3 research rests with the IBC of the institution that houses the investigator. There are several different things that fall under the BSL3+ guidance and that is often dependent upon the agent being used and the types of experiments being used. BSL3+ can require rooms that have shower in/shower out capabilities to provide additional assurances that agents aren't brought out of a facility. Another common BSL3+ addition is the type of respiratory protection being used. BSL3+ research may require items like PAPRs instead of N95 masks to provide even more safety.

b. What are the current protocols to decide to perform research in a biosafety level-3+ labs instead of a biosafety level 4 lab?

The BMBL defines the agents and the biosafety level that is appropriate for using those agents. The IBC at an investigator's institution holds the final approval over what biosafety level an experiment is done at and they utilize the BMBL as the primary guidance. For the most part, a particular agent is given a biosafety designation and then that biosafety designation can be modified for specific experiments. As an example, research with most hantaviruses occurs at BSL3, but animal experiments with hantaviruses that have a particularly high fatality rate have

to be performed at BSL4. If an attenuated strain of an agent exists, that is often assigned a slightly lower biosafety level. All of this is laid out in the BMBL, but again, it is the institution's IBC that approves the experiments, and the IBC can either not approve an experiment, or ask that it be done at a higher biosafety level, given their assessment of the institutions infrastructure and personnel training.

The Honorable Frank Pallone, Jr.

1. How could a 22% cut to the National Institutes of Health's budget affect your field, as well as the broader landscape of scientific research and innovation?

The effect would very much depend on how the cuts were implemented, but I assume there would be a reduction in new research grants being funded as well as a cut to grants that were already approved for funding. For new grants funded through the NIAID, the institute I'm most familiar with, only the top 12% of new R01 proposals are funded. This percentage would certainly be decreased, leading to a reduction in new research grants across all infectious disease disciplines – including those that are currently not considered to be pathogens with pandemic potential. The cut to existing grants would mean that some of the approved research would be cut, leading to reductions in workforce because most laboratory infectious disease workers are funded by NIH grants. NIH budgets have not kept up with the inflation rate seen in biomedical research so investigators are already having difficulty funding projects in a manner that will allow for speedy completion of projects. Research in new initiatives like nasal vaccines or universal coronavirus vaccines would certainly be moving forward at a slower rate because fewer laboratories would be funded to do this work.

2. What scientific breakthroughs have researchers been able to achieve through the research happening in high containment labs?

While there are many important insights scientists have learned about how high containment pathogens infect and cause disease, I think the simplest example is the development of Ebola vaccines. We now have vaccines that have incredibly high efficacy against Ebolavirus mortality

and disease and it was primarily due to the use of Ebolavirus and animal models of Ebolavirus infection – all of which was done in BSL4 labs.

3. What scientific breakthroughs have researchers been able to achieve using enhanced potential pandemic pathogens?

While controversial topics, it is quite clear that work on the transmission of H5N1 viruses and the ability of animal coronaviruses to infect humans have provided important insights into what these viruses. Given the current global increase in H5N1 infections in birds and mammals, it is very clear that work on transmission of H5N1 in ferrets has provided important insights into the types of properties needed for H5N1 to transmit among mammals, along the simple sequencing of viruses to give us insights into how close those viruses are to become a mammalian pathogen. Work with bat coronaviruses has clearly shown that binding to a human cell is not enough to allow for that virus to infect the cells and cause disease. Factors outside of receptor binding – specifically how the virus protein is processed by certain enzymes within a human cell, are incredibly important for allowing bat coronaviruses to jump to humans, and we now can monitor bat virus sequences for those signatures and focus down on the handful of viruses that have high potential for causing human infections.

The Honorable Kathy Castor

1. How have prior funding pauses for research using enhanced potential pandemic pathogens impact the development of flu-related countermeasures and public health preparedness

Prior funding pauses often begin with a very broad group of grants being paused and reviewed. Prior research pauses based on H5N1 influenza or work with bat coronaviruses started with pauses on all influenza and coronavirus work so each grant could be reviewed for potential gain of function work. The review process took several months before work on seasonal influenza viruses and coronaviruses was cleared, most likely because there are a large number of grants to be reviewed and the process had to be thorough and complete. During the 2014 funding pause, my laboratory had work on how influenza vaccines recognized new seasonal influenza viruses

paused, and while my research was paused, the influenza viruses evolved to evade vaccine immunity naturally.