

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
DOCUMENT BINDER
June 15, 2018

**"THE STATE OF U.S. PUBLIC HEALTH BIOPREPAREDNESS: RESPONDING TO
BIOLOGICAL ATTACKS, PANDEMICS, AND EMERGING INFECTIOUS DISEASE
OUTBREAKS"**

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May 15, 2018

The Honorable Robert Kadlec
Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services
200 Independence Ave., SW
Washington, DC 20201

Re: Transforming medical countermeasure technology and partnerships

Dear Dr. Robert Kadlec:

The Blue Ribbon Study Panel on Biodefense recently moderated two roundtables to identify ways to overcome some of the most vexing medical countermeasure (MCM) technology, business, and policy challenges across the biological threat domain. Private sector pharmaceutical, scientific, academic, and governmental affairs representatives attended and were joined at the second meeting by federal officials from the Department of Agriculture (USDA), Department of Defense (DOD), Department of Health and Human Services (HHS), and the White House.

The MCM assets now available to civilians and to military personnel have grown substantially in the last decade. The partnerships needed to continue to build these assets to meet persistent and advancing biological threats, however, are now at considerable risk. Real and perceived under-investment, unsustained investment, process uncertainty, and strategic disparity undermine what must be a vibrant enterprise. We maintain that advancing the national MCM infrastructure needed for research, development, and procurement will reduce the risk associated with biological warfare, bioterrorism, emerging infectious diseases, and biological accidents. We urge you to demonstrate your commitment to this core national security function by advancing the following recommendations.

1. **Integrate animal health into the national security approach to medical countermeasures.** The gross inequality between human and animal funding levels and the segregation of research between the two sectors constitute a national security liability. Many material threats, select agents, and emerging infectious diseases are human diseases with veterinary counterparts, some of which regularly cause outbreaks elsewhere in the world in livestock and wildlife. Yet conversations about the protection of human health by controlling emerging infectious diseases in animal hosts have been extremely limited, and the authority of animal health agencies to regulate has been based on animal health, not public health.
 - a. ***Establish a framework for combatting emerging infectious diseases.*** Most emerging infectious diseases in people originate in animals. No MCM were ready when the largest Ebola outbreak the world had ever seen – likely caused by a spillover from bats to humans – occurred. In the preceding years, the government had not sufficiently determined what to fund with its limited resources. At present, HHS prioritizes efforts to address biological threat agents via Department of Homeland Security material threat determinations (MTDs), but the U.S. government has not instituted and budgeted for an analogous process for emerging infectious diseases. In accordance with Blue Ribbon Study Panel Recommendation 7c (*A National Blueprint for Biodefense*, 2015), HHS, in coordination with DOD and USDA, should create a similar prioritization framework for emerging infectious disease threats. This framework should address pathogens and pathogen families with the potential to cause a catastrophic public health emergency and include agents known to infect wildlife and domestic animals. It should drive funding for MCM development and other areas (e.g., biosurveillance, response planning) and engage and motivate the private sector to develop and manufacture MCM. Funders must establish a vision for an emerging infectious disease MCM enterprise, define what constitutes successful emerging infectious disease MCM, and communicate this vision along with specific product requirements to industry partners.

- b. ***Make USDA part of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE):*** BARDA was envisioned to be part of – not the entire – MCM enterprise. USDA should also participate in PHEMCE. Many diseases that could necessitate USDA MCM acquisitions are the same for DOD and HHS. USDA also has lessons to share about how it works with industry to develop effective MCM for production animals, a market in which the cost must be low and efficacy must be high. Some veterinary companies are already using platforms to develop their animal products, and the veterinary development timeline is much shorter. This means animal health pharmaceutical companies get products to market earlier. These companies also possess extensive experience in areas like animal models and manufacturability that can help inform human MCM endeavors. These experiences are relevant and should not be ignored.
- c. ***Require animal disease risk assessment.*** USDA should develop a risk assessment for animal diseases and work with HHS to assess the risk of diseases with zoonotic potential. USDA should assess the ability of the National Veterinary Stockpile to deploy sufficient MCM to combat high-consequence animal diseases within 24 hours of request. USDA should also use these risk assessments to prioritize the pathogens identified on the USDA *High-Consequence Foreign Animal Diseases and Pests* list. USDA should use the findings to inform its budget request; drive federal priorities for MCM innovation; and incentivize public-private partnerships to develop, transition, approve, license, and procure these products.

2. **Reduce market and process uncertainty at BARDA.** Variability and lack of certainty are two of the foremost hurdles to expanding industry participation in MCM advanced development and manufacturing. Indeed, these hurdles may prove so significant for some companies, even those that have successfully delivered MCM, that they may exit the market entirely. Although all biopharmaceutical ventures carry risk, larger companies can manage this risk through a balanced portfolio of projects, the most successful of which can yield a high return on investment. Pervasive market uncertainty in the far less profitable MCM enterprise makes business endeavors unattractive and unsustainable.

- a. ***Create fiscal certainty.*** In order to develop national security MCM, industry partners forego potential profit margins orders of magnitude higher than for commercial products. These companies need certainty in procurement to convince them and their investors that engaging in MCM development makes reasonable business sense. The annual appropriations process for advanced development and procurement, and dependency on emergency supplemental appropriations for unanticipated threats, make doing business with companies that base their operations on multi-year outlooks and planning unsustainable. In accordance with Blue Ribbon Study Panel Recommendation 28b (*A National Blueprint for Biodefense*, 2015), Congress must reinstate the advanced appropriation for Project BioShield for ten years at a minimum of \$7.1 billion. Additionally, in accordance with Blue Ribbon Study Panel Recommendation 28c, Congress and the HHS Assistant Secretary for Preparedness and Response (ASPR) should address prioritization and the need for guaranteed, sustained funding for pandemic influenza preparedness. The appropriation levels must be tied to rigorously established MCM requirements based on risk analysis.
- b. ***Create process certainty:*** In the last several years, the HHS Biomedical Advanced Research and Development Authority (BARDA) noticeably shifted away from process and partnership toward product. Prioritizing products over partnerships has damaged partnerships and preparedness. The rules governing BARDA and DOD processes for advanced development and manufacturing should be defined with industry partners up front and with far greater clarity and commitment. Companies need to understand when and how much of their proposed product the government will procure, as the frequent moving of goalposts throughout development and procurement creates an untenable business environment. For projects in which the government is not interested, federal public health security leaders need to relay that quickly (i.e., white papers should be reviewed and comment provided within 45 days). The BARDA process at this stage of review should be more like that of the Defense Advanced Research Projects Agency (DARPA), for which program managers, not contracting officers, are the central deciding figures.

3. **Accelerate platform technologies.** One way to create MCM quickly, safely, and effectively for unpredictable emerging infectious diseases and outbreaks is to develop a suite of platform technologies. Generally, platform technologies rely upon a common manufacturing process backbone that uses a standard process to insert foreign genes. By relying upon a well-established manufacturing process and customization through standardized processes, platform technologies can reduce the risk associated with development. These production platforms may be based on, but not limited to, RNA expression systems; DNA cloning vectors; various virus, plant, or

bacterial expression vectors; and viral-vectored vaccines. With targeted government and industry investments, these technologies could come to fruition within three to four years, especially for vaccines and diagnostics. To mature the technology, however, the government must mature the way it invests in the technology and ensure that partnership and business plans accompany technical plans for leveraging any platform capability. There is presently no business model in place that addresses how the government can work with industry to develop MCM platforms. At a minimum, elements of certification, expedited review, and the role of the HHS Centers for Innovation in Advanced Development and Manufacturing must be addressed.

- a. ***Certify platforms:*** The Food and Drug Administration (FDA) approves products, not platforms. FDA, in consultation with DOD, BARDA, and other PHEMCE partners, should establish an MCM platform certification process. A regulatory construct that allows for the consideration of a company's novel platform as a basis for future MCM products would serve as an industry incentive. Its establishment would effectively reduce the risk of future product development using that platform. Determining what constitutes a platform will be difficult, but the definition should include a regularized chemistry, manufacturing, and controls (CMC) process and standardized general release criteria. The USDA Center for Veterinary Biologics policy, "Licensing Guidelines for Production Platform-Based, Non-Replicating, Nonviable Products," allows for rapid swapping of closely related immunogenic determinants, and could provide a starting point from which FDA could build a platform certification process for human products.
 - b. ***Priority review platforms:*** The platform certification process described above is likely to be extensive and should result in a thorough FDA understanding of the platform technology (e.g., CMC, clinical experience). This advanced understanding will enable subsequent review by the FDA under the expedited Priority Review process of other products based upon that certified platform. FDA commitment to the accelerated approval times associated with Priority Review for subsequent products utilizing a certified platform would provide significant incentive for industry to utilize appropriate platform technologies.
 - c. ***Leverage CIADMs:*** The HHS CIADMs and the DOD MCM Advanced Development and Manufacturing facility (ADM) were envisioned to make such platform-based products a reality. They could enable advanced development and manufacturing of platform technologies if aggressively integrated into the product development process. They should become places where companies want to go to advance their promising technologies. They should shrink development schedules and address significant business difficulties. At present, two major challenges prevent this: small companies are concerned about protecting their intellectual property when handed over to a privately owned ADM with its own MCM interests, and large companies are concerned about risks to their commercial business during regulatory review. The Salk Institute, a private nonprofit organization, was essentially the forerunner of what we think of as an ADM today, and BARDA should consider Salk's example as it revisits the business model for these kinds of facilities. DOD and BARDA should undertake planning for CIADM reconfiguration immediately. Planning should include industry and all federal agencies with MCM responsibility. Considerable thought must be given to contracting reform (discussed below) as the Federal Acquisition Regulation (FAR)-based, cost-reimbursable contract system in place does not work. An independent assessment (outside of DOD and HHS) of the existing CIADM model is needed to support this reconfiguration. This planning must consider the role of the USDA and its industry partners in using the CIADMs to enable mutually beneficial technologies and to keep the facilities in use.
4. **Reform FDA process to develop products faster.** We can get closer to on-demand MCM in just a few years and investments to improve production cycling by days or weeks are possible. These kinds of advances, however, will not provide the same near-term relief that FDA could achieved on release testing. Investment in enabling technologies must go, therefore, hand in hand with reform of regulatory process. FDA needs to be part of the advanced development process early on, describing what it wants to see in a product or an investigational new drug. Advances in the speed with which products are marketed should not compromise the FDA's high safety and efficacy standards.
- a. ***Standardize and clarify regulatory process.*** The FDA, in collaboration with its upstream development government partners, must address development and standardization of regulatory processes that will provide needed transparency to MCM developers. The MCM industry needs to understand all elements of the process, and the government needs to mitigate the inherent risk. Several areas of regulatory reform should be considered – for example, reducing risk associated with clinical trials, and allowing companies to

focus their resources on development. Through P.L. 115-92, Congress authorized DOD to request, and FDA to provide, assistance to expedite the FDA review process for MCM for military personnel. DOD and FDA have now put a work plan in place to coordinate planning for this process. FDA and BARDA should develop a parallel plan. Expedited release testing and a plan for increased usage of emergency use authorizations (EUAs) should be addressed as part of this plan.

- b. ***Expedite release testing:*** Even with a vaccine platform, the response time to produce a vaccine for the foreseeable future will be 6-12 months for mass-produced product. While maintaining safety and efficacy standards, acceptable FDA release testing during an outbreak might be different from acceptable release testing at other times. FDA should consider options. For instance, FDA might release products for use on an interim basis with final release testing to follow. FDA might identify suitable surrogates in place of full toxicology panels – or at least utilize a process to pre-identify what those surrogates would be. FDA should describe what an accelerated schedule would look like in an emergency. This will be especially important for platforms that could address multiple infectious diseases. Once in place, manufacturers could then propose specific schedules for a given MCM.
- c. ***Examine increased usage of Emergency Use Authorizations:*** EUAs are designed for those MCM that are sufficiently well characterized to be of likely clinical benefit in an emergency. FDA essentially certifies that a given MCM fulfills EUA requirements. FDA should determine when more aggressive utilization of EUAs would be appropriate.

5. Improve contracting authorities. BARDA must be empowered to make decisions in the best interest of fulfilling its mission. This means ensuring that the contracting process is as smooth, flexible, and transparent as possible. Other Transactional Authority (OTA) is most prominent among the existing contracting authorities that would incentivize MCM partnerships, yet it is utilized very rarely and limited by the statute that provided OTA authority to BARDA.

- a. ***Amend the OTA statute.*** Congress modeled the OTA authority addressed in the *Pandemic All-Hazards Preparedness Act (PAHPA)* after DOD's OTA statute. In its reauthorization of *PAHPA*, Congress should customize OTA authority to fit BARDA's needs. Congress should also remove references to DOD and the need for approval by the senior executive for projects above \$20 million (as it did previously for DOD). OTA contracts should become far more common than they are now, perhaps as common if not more than FAR-based contracts.
- b. ***Adopt OTA for the CIADMs:*** FAR-based contracting does not work for rapid response procurements. Using OTA for the ADMs is critical to prevent abandonment of partnerships when rapidity is imperative, when the science does not go as planned, and when intellectual property and FAR-based requirements arise. DOD has adopted this OTA-based model for its ADM.
- c. ***Move contracting authority back to BARDA.*** In accordance with Blue Ribbon Study Panel Recommendation 29a (*A National Blueprint for Biodefense*, 2015), and the *21st Century Cures Act* Section 3082, contracting authority should be the exclusive responsibility of BARDA, not the office of Acquisition, Management, Contracts and Grants in the Office of the ASPR. This move must be finalized.

6. Foster innovation and new capabilities. The government often bases MCM-related plans on budgets instead of basing budgets on need. A similar mindset is seen with the government's approach to industry, often issuing solicitations to assess existing capabilities, rather than fostering new capabilities to meet national security needs. At the time of its authorization in *PAHPA*, Congress envisioned BARDA to be on the leading edge of MCM innovation. Over the past decade, BARDA has focused on more, well-established, product development technologies and investments in technologies closer to full maturity. This approach certainly justified much of the development portfolio. Live viral vaccine platforms and therapeutics based on monoclonal antibodies may well provide near- to medium-term solutions. Yet BARDA needs to devote sufficient resources to novel and high-risk product development activities in parallel with their less risky investments.

- a. ***Invest in novel and high-risk products.*** Meeting emerging national security threats will require BARDA to employ a high-risk, high-reward model for at least a portion of its investments. Instead of issuing solicitations to assess current industry capabilities, agencies should aggressively work with the private

sector to build capabilities to meet national security needs. While investment in tried-and-true technologies will remain important, aggressively pursuing technologies that fall outside BARDA's comfort zone is imperative. The *21st Century Cures Act* authorized the Director of BARDA to engage an independent, non-profit innovation partner. BARDA should leverage this opportunity to dedicate additional resources to high-risk, high-reward outputs. It should further consider the role of the animal sector in providing needed technological advancements. The animal sector has existing markets for certain pharmaceuticals (for instance, with respect to coronaviruses and influenza viruses, which happen to be the most significant viral pandemic threats to the human population) that are lacking in the human sector. A shared interagency approach to planning for, and funding in, such areas could lead to needed innovative breakthroughs. Precedence for interagency funding mechanisms can be found in the funding HHS provided to USDA in 2009 to conduct domestic biosurveillance for swine influenza virus, a pathogen with minimal health impacts on the animal carrier but large potential impacts on public health.

- b. ***Invest in rapid diagnostics.*** The nation needs to invest far more in patient-side, point-of-care diagnostics. Diagnostics can guide prioritization of MCM resources, but MCM conversations often refer only to vaccines and therapeutics, omitting diagnostics altogether. Rapid diagnostics cannot continue to be an afterthought. In accordance with Blue Ribbon Study Panel Recommendation 30a (*A National Blueprint for Biodefense*, 2015), DOD and BARDA need to invest in rapid diagnostics as a core element of their MCM portfolios. This work should identify generalized biomarkers that would enable such technologies.
- c. ***Drive decision-making with early warning and predictive tools.*** Leadership has yet to embrace predictive science as a core capacity that can support traditional and transformative MCM development. Advances in genomics and proteomics, risk mapping, and biosurveillance data analytics should all be leveraged to create early warning that could both inform and spare the stockpile. Budget requests and corresponding appropriations should support these efforts and ensure that they are an integral part of the federal MCM development and procurement strategy by aligning MCM investments with the threats identified through early warning programs.

7. Establish end-to-end enterprise coordination. Although PHEMCE was envisioned as a coordinating body for the federal MCM enterprise, it has been too HHS-centric to do this effectively. Development of a far more forward-looking process – from idea to procurement to dispensing – is needed. As the Office of the ASPR reimagines the end-to-end nature of the enterprise, it has an opportunity to address some specific challenges in the current construct.

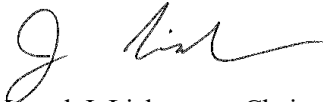
- a. ***Improve interagency product transitions.*** Successful research projects at the National Institutes of Health, DARPA, or other agencies, must begin competition anew for advanced development – if advanced development funding is even available or prioritized. This creates major bureaucratic hurdles to product advancement. The National Biodefense Strategy should direct the creation of more streamlined interagency transition mechanisms. Awards can be structured to assume transition from one agency to the next.
- b. ***Transfer management of the Strategic National Stockpile under specific conditions.*** In the President's Budget Request for FY 2019, the Administration moved management responsibility of the Strategic National Stockpile (SNS) from the Centers for Disease Control and Prevention (CDC) to the ASPR. CDC management of the SNS has been inadequate, resulting in industry confusion and losses when the agency suddenly decided to remove elements from the stockpile that it had previously approved. The Administration made this move, in part, to better enable HHS leadership to direct acquisition for, and deployment of, the SNS. The move has the potential to create a more cohesive development-to-distribution structure and apply more process certainty to procurement decisions. Concerns about how BARDA and the SNS will interact once the move is finalized, and whether investments made by BARDA will inadvertently or intentionally force the SNS to acquire those MCM it developed, must be addressed. Congress should authorize the transfer of management of the SNS to the ASPR only if it also requires the ASPR to fix SNS-related problems that the CDC and state, local, tribal, and territorial (SLTT) partners previously encountered or created, and to put controls in place to prevent automatic uptake of BARDA products by the SNS just to demonstrate BARDA success. Congress should also direct the ASPR to establish a meaningful SNS training program for SLTT partners that focuses on more

than just anthrax, takes SLTT ability to distribute SNS pallets upon receipt into consideration, and does not assume distribution will occur the same as in the military.

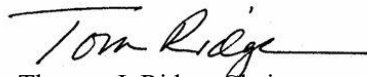
- c. ***Produce an MCM response framework.*** In accordance with Blue Ribbon Study Panel Recommendation 22a (*A National Blueprint for Biodefense*, 2015), the Office of the ASPR, CDC, and the Federal Emergency Management Agency should, together with non-federal partners, identify requirements and capacities needed to achieve successful distribution and dispensing of MCM from the SNS as well as from local caches. The framework they develop must address unresolved issues. A progressive and innovative approach should push beyond what a given agency might devise and the bureaucratic impediments associated with a federal-only distribution system. If implementation exceeds funding available through current grant allocations, additional funding must be requested.

Thank you for considering these findings and recommendations. Please contact Dr. Asha M. George, Panel Executive Director, at (202) 974-2416 or Asha.George@BiodefenseStudy.org with further questions.

Sincerely,



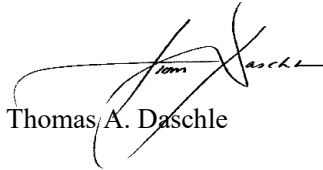
Joseph I. Lieberman, Chair



Thomas J. Ridge, Chair



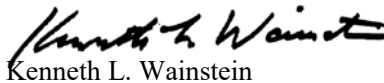
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Minority (202) 225-3641

December 23, 2015

The Honorable Nicole Lurie, M.D., M.P.H.
Assistant Secretary for
Preparedness and Response
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Dr. Lurie,

Pursuant to Rules X and XI of the U.S. House of Representatives, the Committee on Energy and Commerce is examining the adequacy of the stockpile of pre-pandemic vaccines.

The national vaccine goals for pandemic influenza preparedness call for pre-pandemic vaccine stockpiles to protect 20 million people as well as for manufacturing infrastructure to support rapid production of 600 million doses. At a recent National Academies of Sciences workshop, one industry official noted the dynamic nature of the influenza threat and questioned the match of vaccine stockpiles that were purchased 10 years ago against today's circulating strains.¹ For example, the H5N1 influenza emerging in Egypt in 2015 is not necessarily the H5N1 strain that emerged in Vietnam in 2004.

During the November 19, 2015 hearing before the Subcommittee on Oversight and Investigations, Dr. Robin Robinson, the Director of the Biological Advanced Research and Development Authority (BARDA) told the Subcommittee on Oversight and Investigations that BARDA is currently testing stockpiled pandemic influenza vaccines. We would be interested in the test results to determine whether the vaccines would provide protection against the circulating avian flu viruses which devastated U.S. poultry this year. These results would be helpful to the committee in understanding whether the vaccines are protective. At a June 2015 meeting of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP), a CDC official said tests showed that neither H5N8 nor N5N2 viruses cross-reacted with an H5N1 vaccine, suggesting that the vaccine would not be protective.

¹ The National Academies of Science, Rapid Medical Countermeasure Response to Infectious Diseases: Enabling Sustainable Capabilities Through Ongoing Public- and Private-Sector Partnerships, Workshop Summary (2015).

² In an interview, Dr. Robinson stated that BARDA's stockpile contained some doses based on a strain called Anhui that is more closely related to H5N8 and H5N2, and that the CDC planned to test whether the Anhui-based H5N1 vaccine would offer any protection against the other avian strains.³

There is a need to ensure that the pre-pandemic vaccine stockpile is protective. Earlier this year, the World Health Organization stated the unprecedented number of currently circulating new avian and swine influenza strains is "ominous." Two new highly pathogenic strains of avian flu (H5N8, H5N2) are circulating in the U.S., and they have already caused the death of nearly 50 million birds at a cost of \$1 billion to our economy. A health alert issued by CDC on June 2, 2015 notified public health workers and clinicians of the potential for human infection with these viruses, and made recommendations for patient investigation, testing and infection control. If these strains were to make the jump to humans, pandemic risk would increase. These developments heighten our interest in assuring the United States is sufficiently prepared for pandemic influenza.

Innovation, stockpiling and building infrastructure capacity for a rapid medical counter measure (MCM) response to pandemic influenza threats is managed primarily by BARDA programs. From 2005 to 2013, pandemic flu preparedness was funded through a \$5.6 billion emergency advanced appropriation, averaging \$750 million per year. Funding has shifted to annual appropriations at significantly lower amounts and BARDA's pandemic flu program only received \$72 million in Fiscal Year 2015. As a result, HHS has raised an issue of whether BARDA can continue to support the efforts required to prepare for the next pandemic. The FY16 HHS budget request said the following: "This FY 2015 reduction below the request level impedes HHS' ability to maintain existing programs for pre-pandemic influenza vaccine stockpiling and development of influenza antiviral drugs and immunotherapeutics, which are central programs to address critical vulnerabilities for U.S. pandemic preparedness."

While vaccines for seasonal influenza change year-to-year, BARDA maintains a stockpile of roughly \$1.75 billion worth of pandemic influenza vaccine. This year, however, BARDA has only budgeted about \$20 million – or 1 percent of the stockpile value – for replenishment and maintenance of this asset.

To assist the committee's oversight, please respond to the following questions by January 12, 2016:

1. What are the results of testing BARDA has done on stockpiled pandemic vaccines? Please provide the committee with a list of the tests and the most recent data collected from these tests. How does BARDA evaluate these results in the context of the periodic risk assessments conducted by the HHS Influenza Risk Management Working Group or other HHS experts?

² Robert Roos, "BARDA: Recent 'universal' flu vaccine proposals fell short," CIDRAP News (July 23, 2015).

³ Id.

2. BARDA's testimony discussed BARDA's plans to also test these stockpiles for potency. What were the results of these tests? Were any additional tests conducted to determine if the vaccines in the stockpile are well-matched to the current threats?
3. In your July 31, 2015 letter to the committee, you wrote that "[a]s a direct outcome of the IRAT (Influenza Risk Assessment Tool) process, the agencies [ASPR/BARDA and CDC] are conducting multiple scientific studies to determine whether previously stockpiled H5N1 vaccines confer immunity against HPAI [Highly Pathogenic Avian Influenza] H5 viruses in humans." Are any of the studies completed? If so, what were the findings? If not, when are the studies expected to be completed?
4. What is the status of efforts by HHS agencies and vaccine manufacturers to develop, manufacture, and test new vaccine candidates to H5N2 and/or H5N8 viruses using egg- and cell-based influenza vaccine platforms to supplement existing stockpiled vaccines?
5. Are there any studies that show the effects of long-term storage on the potency of influenza vaccines? If yes, what do the studies show? If not, what is the basis for our understanding about the potency of influenza vaccines? At what point, would the vaccines start to lose potency?
6. What kind of testing of the pre-pandemic stockpile is needed on an ongoing basis and what funding is needed to support this kind of testing?
7. At the CDC's ACIP meeting in June 2015, a CDC official showed data indicating that the stockpiled vaccines do not protect against the current circulating avian strains, and may be distantly related to the viruses. How many doses of vaccine are in the BARDA stockpile contain the Anhui strain that is more closely related to the currently circulating avian strains? Has there been any testing of the vaccines with the Anhui strains on how well they protect against the currently circulating avian strains?
8. What assumptions is BARDA using to determine if/how well the current pre-pandemic stockpiles will protect the public in the event of a pandemic?
9. How do issues like the age of the stockpile and possible mismatch against currently circulating pandemic strains affect these determinations?
10. Are pandemic influenza risk assessments provided to key stakeholders?
11. Given that existing contingency pandemic influenza vaccine stockpiles are aging – most are 5-10 years old – what resources does BARDA need on an annual basis to update the stockpile and prepare for the next pandemic threat?

12. If a rapid MCM response was required to address a seasonal influenza epidemic due to a mismatched vaccine, does BARDA have resources to respond? If so, how? Are resources available to support availability of a matched vaccine?
13. How does BARDA plan to maintain and replenish the stockpile of influenza vaccines, some of which are now a decade old? What funds are planned to be used?
14. Are current stockpiles consistent with the national Strategy for Pandemic Influenza which states the U.S. should have "sufficient vaccine to vaccinate the entire U.S. population within six months of the emergence of a virus with pandemic potential"?
15. What level of annual funding would be sufficient, going forward, to maintain and replenish the stockpile, in order to ensure U.S. preparedness against pandemic influenza? Please detail how these funds would be spent.

If you have any questions, please contact Alan Slobodin of the majority committee staff at (202) 225-2927 or Una Lee with the minority staff at (202) 225-3641.

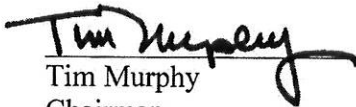
Sincerely,



Fred Upton
Chairman



Frank Pallone Jr.
Ranking Member



Tim Murphy
Chairman
Subcommittee on Oversight
and Investigations



Diana DeGette
Chairman
Subcommittee on Oversight
and Investigations

Attachment



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Assistant Secretary for
Preparedness & Response
Washington, D.C. 20201

03/15/16

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your letter concerning our nation's stockpile of pre-pandemic vaccines. As the Assistant Secretary for Preparedness and Response (ASPR) within the Department of Health and Human Services (HHS), I appreciate the Committee's attention and commitment to preparedness and response issues, particularly related to pandemic influenza among many other important issues. While I missed the opportunity to testify before the Subcommittee on Oversight and Investigations on November 19, 2015, I am grateful Dr. Robin Robinson, ASPR's Director of the Biomedical Advanced Research and Development Authority (BARDA), was able to speak on my behalf and answer your questions.

As addressed in the hearing entitled, "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?" influenza viruses can be difficult to predict and manage. Rest assured, the Department takes all influenza virus threats very seriously. We manage a multi-pronged approach to prepare for the emergence of new viruses and to thwart the potential spread of influenza to humans from poultry and other animals. Moving forward, advances in vaccines, new antiviral medications, and new diagnostic tests are just some of the ways HHS and ASPR have taken on the challenge of pandemic influenza preparedness. Likewise, public-private partnerships with industry have also led to cost savings and a surge in the nation's ability to produce vaccines and drugs for influenza and other health threats.

The safety and well-being of the American people is of the utmost importance. I thank you again for the opportunity to address your questions and I look forward to continuing our work with you and the Committee towards this important goal.

With that said, I have enclosed detailed responses to the questions in your letter. If you have any additional questions, please do not hesitate to contact me.

Sincerely,

Nicole Lurie, MD, MSPH

Enclosure

- 1. What are the results of testing BARDA has done on stockpiled pandemic vaccines? Please provide the committee with a list of the tests and the most recent data collected from these tests. How does BARDA evaluate these results in the context of the periodic risk assessments conducted by the HHS Influenza Risk Management Working Group or other HHS experts?**

Potency and sterility assays are used for all influenza vaccines licensed in the United States (U.S.) by the Food and Drug Administration (FDA). Potency and product sterility tests are performed on bulk and final product vaccine antigens and adjuvants throughout the national pre-pandemic influenza vaccine stockpiles managed by ASPR/BARDA. The influenza vaccine antigen potency assay, which measures the amount of active hemagglutinin protein - the major viral component conferring immunity - is performed by each manufacturer and the FDA using a serial radial immunodiffusion assay (SRID) specific for each influenza vaccine strain (e.g., A/H5N1/2004/Vietnam). These tests are conducted at three- to six-month intervals by three vaccine manufacturers [Sanofi Pasteur, GlaxoSmithKline (GSK), and Commonwealth Serum Laboratories (CSL, formerly Novartis Vaccines Division)]. The adjuvant potency assays measure the amount of active molecules (e.g., squalene and vitamin E) in the adjuvant that stimulate immunity. They are performed by the manufacturers using high-performance liquid chromatography (HPLC) and photometry tests specific for each of the stockpiled oil-in-water emulsion adjuvants (AS03 and MF59).

The most-recent test results in 2015 (**Table 1**) show that the potency and sterility of the stockpiled A(H5N1) and A(H7N9) vaccine antigens and MF59 and AS03 adjuvants are acceptable for formulation into final vaccine products, if needed, as there is enough stockpiled vaccine antigen and adjuvant to immunize at least 20 million persons against each vaccine strain.

In addition, the National Institutes of Health (NIH), through the National Institute of Allergy, Immunology, and Infectious Diseases (NIAID) has continued to conduct a series of clinical trials of stockpiled H5N1 and H7N9 vaccines with and without MF59 and AS03 adjuvants. While the primary focus of the NIAID clinical trials has been to assess different vaccination strategies and to advance our understanding of the breadth and duration of the immune response, the clinical study results also show that these stockpiled vaccines continue to be well tolerated and immunogenic in humans.

ASPR/BARDA and other HHS agencies routinely review the results of risk assessments using the Centers for Disease Control and Prevention's (CDC) Influenza Risk Assessment Tool (IRAT) on newly emerged novel influenza viruses with pandemic potential. Pandemic risk is based on two risk scenarios: emergence (acquiring the ability to spread easily and efficiently in people) and the public health impact (potential severity of human disease caused by the virus and the burden on society after emergence). The IRAT focuses on virological assessment and prioritization and more closely aligns with a multi-criteria or multi-attribute decision analysis approach. The risk elements addressed in the IRAT are listed below.

- **Properties of the virus**
 - Transmission in lab animals
 - Receptor binding
 - Genomic variation
 - Antiviral treatment susceptibility/resistance
- **Attributes of the population**
 - Antigenic relationship to vaccine candidates
 - Existing population immunity
 - Disease severity and pathogenesis
- **Ecology and epidemiology**
 - Human infections
 - Infection in animal species

The Influenza Risk Management group evaluates the vaccine potency results of stockpiled material, the antigenic relatedness of stockpiled vaccines to new influenza viruses, and the IRAT results for severity (impact) and transmissibility of new influenza viruses. These assessments inform decision makers on whether or not to replenish existing vaccine stockpiles, add additional vaccine, or include new candidate vaccine viruses.

Table 1. Results of potency and sterility assays in 2015 for bulk influenza vaccine antigens and adjuvants in the U.S. national pre-pandemic influenza vaccine stockpile.

Product	Manufacturer	Potency Assay Results	Sterility Assay Results ¹
Vaccine Antigens			
A/H5N1/ Vietnam/1203/ 2004	sanofi pasteur Novartis	56% 55-58%	Negative Negative
A/H5N1/Indonesia/05/2005	sanofi pasteur GSK	89% 78-100%	Negative Negative
A/H5N1/Bar Headed Goose/Qinghai Lake/1/2005	sanofi pasteur	57%	Negative
A/H5N1/Anhui/2008	Novartis	57%	Negative
A/H7N9/Shanghai/2013	sanofi pasteur GSK Novartis	75% 80% 60%	Negative Negative Negative
Adjuvants			
MF59	Novartis	Within specifications	Negative

AS03	GSK	Within specifications	Negative
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¹ Sterility result definitions for 14-day standard growth assay. Positive result indicates contamination observed. Negative result indicates no contamination observed.

- 2. BARDA's testimony discussed BARDA's plans to also test these stockpiles for potency. What were the results of these tests? Were additional tests conducted to determine if the vaccines in the stockpile are well matched to the current threats?**

Please see the response to question 1 regarding the test results of vaccine potency, specifically **Table 1**. CDC routinely performs antigenic and genetic characterization of circulating influenza viruses. When new influenza viruses emerge, CDC conducts further studies using reference animal-sera to evaluate how similar these viruses are to those represented by stockpiled vaccines. Typically, when antigenic differences are observed, this prompts the development of a Candidate Vaccine Viruses (CVV) that would provide better protection against the novel virus.

- 3. In your July 31, 2015 letter to the committee, you wrote that "[a]s a direct outcome of the IRAT (Influenza Risk Assessment Tool) process, the agencies [ASPR/BARDA and CDC] are conducting multiple scientific studies to determine whether previously stockpiled H5N1 vaccines confer immunity against HPAI [Highly Pathogenic Avian Influenza] H5 viruses in humans." Are any of the studies completed? If so, what were the findings? If not, when are the studies expected to be completed?**

In 2015, CDC evaluated whether or not stockpiled vaccine antigens (A/H5N1/Indonesia/05/2005 or A/H5N1/Anhui/01/2005) when combined with an adjuvant induced cross-reactive antibody responses to H5Nx viruses. This evaluation used a homologous prime-boost vaccination strategy (i.e., persons received two doses of the same vaccine). Minimum to no cross-reactive antibodies for A(H5N8) and A(H5N2) viruses were detected by microneutralization assays with sera from three H5N1 vaccine clinical studies (two A/H5N1/Indonesia/05/2005 studies and one A/H5N1/Anhui/01/2005 study).

In more recent studies, CDC evaluated whether or not stockpiled H5N1 vaccines (A/H5N1/Anhui/01/2005 and A/H5N1/Vietnam/1203/2004) produced cross-reactive antibody responses to newly emerging A(H5N2) and A(H5N8) viruses (clade 2.3.4.4) using a heterologous prime-boost vaccination strategy. Following one or two doses of non-adjuvanted A(H5N1) vaccine (A/H5N1/Vietnam /1203/2004) as a primer and one dose of adjuvanted A(H5N1) vaccine (A/H5N1/Anhui/1/2005) as a booster, modest levels of cross-reactive antibody responses to A(H5N8) and A(H5N2) viruses were detected. These results suggest that vaccinations primed with an older version of stockpiled H5N1 vaccines and an added booster A/Anhui/1/2005 vaccine, may elicit potentially cross-protective responses against the recent HPAI H5N8/H5N2 viruses. CDC has initiated vaccination and challenge studies using ferrets to determine if stockpiled vaccines will protect against the A(H5N8)/A(H5N2) viruses, and the results of these experiments will be available March 2016.

ASPR/BARDA submitted an Investigational New Drug (IND) application to the FDA on November 20, 2015, for a clinical study to determine whether previously stockpiled vaccines [A/H5N1/Vietnam/1203/2004] manufactured in 2005 and 2007 with MF59 adjuvant manufactured in 2009 and 2013 are still immunogenic. The FDA reviewed and accepted the IND application. The clinical study is set to start in March 2016. Preliminary interim results on immunogenicity should be made available by July 2016. Sera from subjects immunized with different amounts of the older and newer H5N1 vaccine and adjuvant lots will be used in hemagglutination inhibition assays and microneutralization assays to determine the relative antibody levels elicited to homologous vaccine virus (A/H5N1/Vietnam/1203/2004) and other H5N1 viruses.

NIH/NIAID has continued to conduct clinical trials to assess the safety and immunogenicity of stockpiled H5N1 and H7N9 vaccines administered with and without adjuvants. Several studies have been completed and published, while others are ongoing (please also see response to question 1).

4. What is the status of efforts by HHS agencies and vaccine manufacturers to develop, manufacture, and test new vaccine candidates to H5N2 and/or H5N8 viruses using egg- and cell-based influenza vaccine platforms to supplement existing stockpiled vaccines?

CDC developed a recombinant candidate vaccine virus specific to the North American A(H5N8) HPAI viruses that emerged in late 2014 and the A(H5N2) HPAI viruses that caused widespread poultry outbreaks in spring and summer 2015. The A/gyrfalcon/Washington/41088-6/2014 (H5N8)-like "IDCDC-RG43A" virus is the recombinant A(H5N8) candidate virus that represents the viruses found in North America in 2014-2015. It was recommended for development by the World Health Organization. CSL, under contract to ASPR/BARDA, prepared clinical investigational lots of the H5N8 vaccine candidate. These will be released when SRID potency assay reagents become available.

CDC developed candidate vaccine viruses (CVVs) to the A(H5N2) viruses, which caused the majority of poultry outbreaks across the U.S. in 2015. This candidate vaccine virus "IDCDC-RG47B" is an A/gyrfalcon/Washington/41088-6/2014-like virus developed to express the H5 hemagglutinin and the N2 neuraminidase genes from representative A(H5N2) viruses found in North America in 2015. Complete characterization of this virus, including ferret pathotyping, is in progress. If the CVV passes characterization CSL will produce clinical investigational lots in 2016 for future clinical studies.

NIH/NIAID, through its clinical research network, is preparing to start clinical trials to assess the safety and immunogenicity of different concentrations of an H5N8 vaccine administered with and without adjuvants in the second quarter of 2016.

5. Are there any studies that show the effects of long-term storage on the potency of influenza vaccines? If yes, what do the studies show? If not, what is the basis for our

understanding about the potency of influenza vaccines? At what point, would the vaccines lose potency?

Yes, potency studies have been performed continuously on all lots of stockpiled, pre-pandemic H5N1 and H7N9 vaccine antigens. These studies have been performed since the lots were manufactured and will continue. The results of these potency assays have indicated that some of the influenza vaccine antigens (e.g., A/H5N1/Vietnam/1203/2004) undergo an initial diminution (20-25 percent) of potency within the first three to six months then stabilize with gradual losses in potency over years (Fig. 1). However, the vaccine potency of other A(H5N1) strains (e.g., A/H5N1/Indonesia/05/2005) decrease very slowly and retain nearly all of its original potency (Fig. 1). The vaccine virus, the manufacturer, and the manufacturing process affect the potency of stockpiled A(H5N1) vaccines.

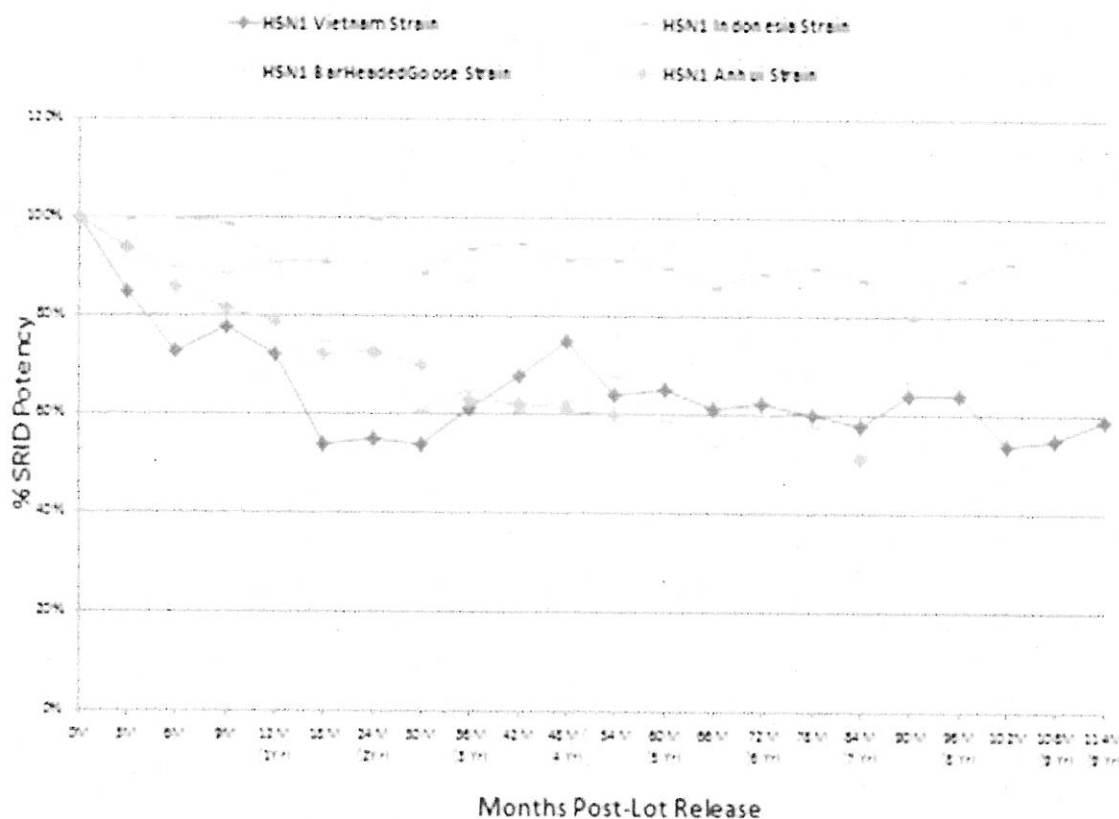


Figure 1. Vaccine SRID potency assay results of stockpiled H5N1 vaccine antigens from 2006–2015.

6. What kind of testing of the pre-pandemic stockpile is needed on an ongoing basis and what funding is needed to support this kind of testing?

Potency and sterility testing of stockpiled bulk and final container vaccine antigens and adjuvants are performed on three- to six-month intervals throughout the storage of these products. Vaccines are tested periodically in animal and clinical studies. Funding (\$1 million to \$2 million per year) for potency and sterility testing of these products at the vaccine manufacturers is provided by HHS through ASPR/BARDA contracts using pandemic influenza supplemental appropriations (2005), H1N1 supplemental appropriations (2009), or annual pandemic influenza funds (2013-2015). Animal and human serology studies (\$200,000 to \$250,000 per study) are conducted at CDC using annual CDC funds. Clinical studies (\$2 million to \$5 million per study) are performed by NIH/NIAID, BARDA's Clinical Study Network, or vaccine manufacturers using supplemental or annual funds, depending on the fiscal year during which the study is performed.

7. At the CDC's ACIP meeting in June 2015, a CDC official showed data indicating that the stockpiled vaccines do not protect against the current circulating avian strains, and may be distantly related to the viruses. How many doses of the vaccine are in the BARDA stockpile contain the Anhui strain that is more closely related to the currently circulating avian strains? Has there been any testing of the vaccines with the Anhui strains on how well they protect against the currently circulating avian strains?

Recent outbreaks of HPAI viruses in U.S. poultry (December 2014 to June 2015) have raised public health concerns. Three novel subtypes of viruses [A(H5N8), A(H5N2), and A(H5N1)] have been identified in infected birds in the U.S. All three subtypes have a Eurasian (HA) lineage and are designated as H5Nx (clade 2.3.4.4). In 2015, CDC evaluated whether or not stockpiled vaccine antigens (A/H5N1/Indonesia/05/2005 or A/H5N1/Anhui/01/2005) when combined with an adjuvant induced cross-reactive antibody responses to H5Nx viruses. This evaluation used a homologous prime-boost vaccination strategy (i.e., persons received two doses of the same vaccine). Minimum to no cross-reactive antibodies for A(H5N8) and A(H5N2) viruses were detected by microneutralization assays with sera from three H5N1 vaccine clinical studies (two A/H5N1/Indonesia/05/2005 studies and one A/H5N1/Anhui/01/2005 study).

In more recent studies, CDC evaluated whether or not stockpiled H5N1 vaccines (A/H5N1/Anhui/01/2005 and A/H5N1/Vietnam/1203/2004) produced cross-reactive antibody responses to newly emerging A(H5N2) and A(H5N8) viruses (clade 2.3.4.4) using a heterologous prime-boost vaccination strategy. Following one or two doses of non-adjuvanted A(H5N1) vaccine (A/H5N1/Vietnam/1203/2004) as a primer and one dose of adjuvanted A(H5N1) vaccine (A/H5N1/Anhui/1/2005) as a booster, modest levels of cross-reactive antibody responses to A(H5N8) and A(H5N2) viruses were detected. These results suggest that vaccinations primed with an older version of stockpiled H5N1 vaccines and an added booster A/Anhui/1/2005 vaccine, may elicit potentially cross-protective responses against the recent

used to develop, manufacture, test, and stockpile vaccines. In our multi-year budget for influenza, we estimate that \$50 million a year may be needed to maintain these stockpiles for fiscal years 2018 and 2019. This money would be used to replace existing vaccine antigens and adjuvants and to address any new vaccines that may need stockpiling.

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
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WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3641
August 11, 2016

Dr. Thomas Frieden
Director
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333

Dear Dr. Frieden:

Pursuant to Rules X and XI of the U.S. House of Representatives, the Committee is examining the CDC's Laboratory Response Network (LRN), a national network of local, state, and federal public health, food testing, veterinary diagnostic, and environmental testing laboratories that provide the laboratory infrastructure and capacity to respond to biological and chemical terrorism, and other public health emergencies. The more than 150 laboratories that make up the LRN are affiliated with federal agencies, military installations, international partners, and state/local public health departments.

Protecting the nation against a potential bioterrorism event is a high priority. To support this effort, the CDC LRN was established and became operational in 1999. The goal of the CDC Laboratory Response Network was to ensure that the nation has appropriate coverage and rapid detection technology and assays to quickly test suspicious materials and detect potential events suspected to be a result of bioterrorism in a timely manner to initiate immediate clinical intervention, surveillance, initiation of post-exposure prophylaxis, and other public health measures such as quarantine to save lives. The Project BioShield Act of 2004 was enacted with \$5.6 billion in funding to procure and stockpile appropriate medical countermeasures to support such medical mitigation.


The key to a successful response to a potential bioterrorism event relies on our ability to rapidly detect and diagnose suspected clinical cases. This task was clearly assigned to the CDC LRN for implementation and preparation of this aspect of the nation's biodefense. As part of the Committee's overall oversight of biodefense preparedness, the Committee seeks information about the current capabilities of the CDC LRN.

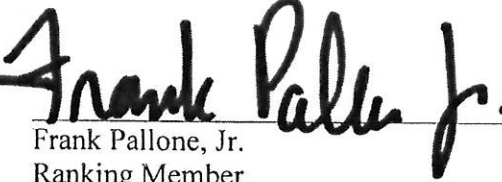
To assist the Committee, please provide the following information by August 25, 2016:

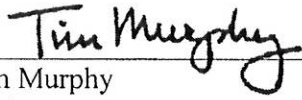
1. How many CDC LRN labs are there in the U.S.? What is their current capability to rapidly detect select agents and toxins?
2. How many assays have been developed to date to support this critical mission and when were they developed and deployed?
3. How many of the select agents and toxins are the CDC LRN laboratories across the nation capable of detecting?
4. What are the types of assays (PCR, ELISA, Culture, etc.) developed by CDC LRN and deployed? Please provide details as to the agent, the type of assays, their limit of detection, etc.
5. Please provide a detailed description of the process for qualifying any assay for deployment in the CDC LRN. Please provide details as to what each component or group within CDC or in partnership with other agencies contribute to this effort.
6. How many assays were developed and deployed through the Public Health Actionable Assay Program in collaboration with the Department of Homeland Security Science and Technology Directorate (S&T)?
7. Please explain the roles and responsibilities between DHS S&T and HHS CDC relating to the Public Health Actionable Assay Program.
8. Does the CDC LRN have the capability to detect emerging infectious diseases (e.g., Zika, MERS, Ebola, Novel Influenza, Chikungunya)? If so, how many CDC LRN labs across the nation have such capabilities at the current time? Please provide specific details as to the agent, the type of assay, and the labs that have the capability.
9. Do all of the CDC LRN labs have equivalent capability? If not, please provide the number of labs with their specific capability.

If you have any questions regarding this request, please contact Alan Slobodin with the Energy and Commerce Majority staff at (202) 225-2927, or Elizabeth Letter with the Energy and Commerce Minority staff at (202) 225-3641.

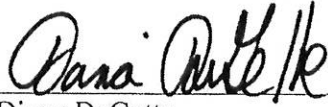
Sincerely,


Fred Upton
Chairman
Committee on Energy and Commerce


Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce

A handwritten signature in black ink, reading "Tim Murphy". The signature is written in a cursive style with a large, stylized "M".

Tim Murphy
Chairman
Subcommittee on Oversight and
Investigations

A handwritten signature in black ink, reading "Diana DeGette". The signature is written in a cursive style with a large, stylized "D".

Diana DeGette
Ranking Member
Subcommittee on Oversight and
Investigations

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS
Congress of the United States
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2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3641
October 26, 2016

Dr. Thomas Frieden
Director
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333

Dear Dr. Frieden:

Thank you for your September 10, 2016 response to our letter requesting information about the current bioterrorism preparedness capabilities of the Centers for Disease Control and Prevention's (CDC) Laboratory Response Network (LRN).

We have follow-up questions to your letter's answers to specific questions raised in our letters. Pursuant to Rules X and XI of the U.S. House of Representatives and to assist the Committee's continuing examination of the LRN, please provide the following information by November 9, 2016:

1. In response to Question 1, your letter sets out two tables providing current capability information for LRN laboratories to detect select agents and toxins.
 - a. With regard to the table, "Number of LRN Reference Laboratories Capable of Detecting Select Agents and Toxins," only some of the select agents/toxins that are a severe threat to human health are listed. Please explain why the CDC LRN does not have assays for all of the select agents and toxins listed by FSAP to be a severe threat to human health. Does the CDC LRN have assays for all of the agents identified by a material threat determination (MTD) from the Secretary of Health and Human Services? Please provide details on the assays for each MTD agent, and if there is no assay for an MTD agent, please explain why not.
 - b. With regard to the table, "Limit of Detection for LRN Real-time PCR Assays," are the assays listed in this table less sensitive than culture-based assays?
2. In response to Question 2, your letter stated that the LRN developed and deployed a rapid assay for the detection of *Coxiella burnetii* and *C. botulinum toxin*, and a second rapid

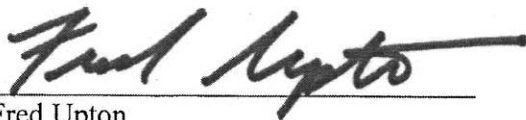
- assay for detection of *Zaire ebolavirus*. Have any of these assays been fully approved by FDA? If not, why not? Why is it that CDC has only developed and deployed two new assays for three agents over the last 13 years? What about assays for the other agents?
3. In response to Question 3, your letter stated that LRN Reference Laboratories are capable of rapid detection for nine select agents and two toxins. Why only nine agents and two toxins? Why not all select agents and toxins that are listed as a severe threat to human health?
 4. In response to Question 5, your letter mentioned several follow-up questions and requests.
 - a. Your letter stated that "CDC regularly reviews information on potential biological threat agents and emerging infectious diseases to determine the need for development of diagnostics assays for the LRN." Based on the reviews CDC has done, what are the agents CDC has determined to have the need for rapid assays?
 - b. Your letter further noted that evidence suggesting the emergence of an agent as a natural disease threat [e.g., severe acute respiratory syndrome, Middle Eastern respiratory syndrome (MERS), monkeypox, Ebola virus, Zika virus]. Does the CDC have FDA-approved assays for each of these agents in the LRN? If not, why not?
 - c. Your letter stated that "[a]gents are chosen for LRN test development when a test is needed in the public health system based on consideration of" several factors. Please provide the assessments and the associated results.
 - d. Your letter stated that the CDC also works in partnership with the Department of Homeland Security (DHS) to develop assays that meet the sensitivity and specificity requirements of the Public Health Actionable Assay (PHAA) system. Please provide documentation showing how CDC works with DHS on sensitivity and specificity requirements of the PHAA system.
 - e. Your letter stated that "[w]hen a proposal for a specific assay has been developed, it is submitted to the LRN Program's Design Control Process." What is the LRN Program's Design Control Process? Please provide documentation showing how many assays have gone through the LRN Program's Design Control Process.
 - f. Your letter stated that: "In addition to filling a gap in preparedness, several other factors are considered in the decision to develop and deploy an assay, including cost of development and sustainability of the assay, ability to manufacture and quality assure the assay, suitability for LRN's testing platforms." Please provide documents for these assessments conducted for each assay and the findings.
 5. In response to Question 6, your letter raises several follow-up questions.
 - a. Your letter stated that assays for detection of *variola major*, *Rickettsia rickettsia* and *Rickettsia prowazekii*, have been developed in collaboration with DHS, CDC
-

SMEs, and the LRN Program according to PHAA standards. When were each of these assays developed? Please provide dates.

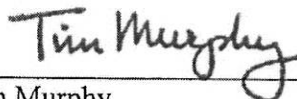
- b. Your letter stated that assays for *F. tularensis* and *Y. pestis* have been developed by DHS according to PHAA standards and are planned for deployment to the LRN after completion of additional studies. When were these assays developed? Please provide dates. Please describe what additional studies CDC will be conducting, when these studies are expected to be completed, and when will these assays be deployed?
 - c. Your letter stated that assays for Ebola virus and Marburg virus have been developed by DHS according to PHAA standards and have been or are in the process of being transitioned to CDC for evaluation of performance and consideration for deployment to the LRN. Has DHS advised the CDC on when the assays for Ebola and Marburg viruses will be transitioned to CDC? If so, when will these assays be transitioned to CDC?
6. In response to Question 7, your letter stated that DHS Science and Technology works in partnership with CDC to develop assays for high-priority threat agents for possible use in LRN." Please provide the reports provided by DHS to date. Your letter stated that "CDC performs in-depth studies of the assays and determines requirements for acceptable criteria for performance and deployments to LRN laboratories." Please provide the reports for which CDC has conducted in-depth studies.
7. In response to Question 8, your letter noted eighty-three public health and military LRN Reference laboratories have the capability to detect Zika, dengue, and chikungunya using a multiplexed real-time (RT) PCR assay; Twenty-five public health and military LRN Reference laboratories have the capability to detect MERS using an RT-PCR assay; and forty-one public health and military LRN Reference laboratories have the capability to rapidly detect *Zaire ebolavirus*. Are all of the assays FDA-approved assays? If not, which ones are not FDA-approved and why are they not approved? Please provide reports for all of these assays along with the documentation associated with the LRN Program's Design Control Process.

If you have any questions regarding this request, please contact Alan Slobodin with the committee staff at (202) 225-2927.

Sincerely,



Fred Upton
Chairman



Tim Murphy
Chairman
Subcommittee on Oversight
and Investigations



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

SEP 09 2016

Dear Mr. Chairman:

Thank you for your letter of May 18, 2016, cosigned by Mr. Murphy, Chairman of the Subcommittee on Oversight and Investigations, regarding laboratory safety and security at the Food and Drug Administration (FDA or the Agency). Laboratory safety and security is one of our highest priorities at FDA and we are fully committed to ensuring the safety of our laboratory scientists, the employees of FDA, and the surrounding community.

We appreciate the opportunity to respond to your questions, and have restated them below in bold, followed by FDA's responses.

- 1. What level of funding and staffing for the Office of Laboratory Science and Safety will the FDA commit to for the next fiscal year budget? Please explain the justification for the level of funding and staffing.**

FDA's Office of Laboratory Science and Safety (OLSS) provides leadership, oversight, and coordination of laboratory policies and operations across FDA to ensure laboratory safety and security. In FY 2017, consistent with the President's Budget, OLSS will receive \$5.2 million in support to cover 13 full-time employees (FTEs) – one senior executive office director, four GS-15 level positions, five GS-14 level positions, two GS-13 level positions, and one GS-11 level position – as well as operational costs. This level of support will allow OLSS to continue to make progress on achieving FDA's goals of augmenting, consolidating, and standardizing laboratory safety and security at FDA.

- 2. Does FDA agree with the ELSW recommendation that the sources of funding should be independent from other FDA centers or offices? If so, will the FDA commit to independent funding for the Office of Laboratory Safety?**

FDA believes that OLSS should have a dedicated level of funding to allow for proper oversight of FDA's labs. OLSS will sit in the Commissioner's Office, and will be managed and operated independently from the other Centers and Offices. FDA will work with existing funding in FY 2016 and funding received in FY 2017 to fund OLSS. FDA is working to determine the long-term resource requirements needed for this important priority.

3. In accordance with the ELSW recommendation, will the FDA commit to having the Director of Lab Safety report directly to the FDA Commissioner?

As previously shared, ensuring the safety and security of our laboratory scientists, employees, and the public at large is one of our highest priorities at FDA. To support FDA with this critical mission, FDA will realign OLSS such that the Director of OLSS will report directly to the Commissioner. OLSS will serve as the Agency's coordinator and lead for implementation of policies and procedures, centralized training, and oversight for operations of all laboratory science, safety, and security related activities. OLSS will work very closely with the Office of the Chief Scientist, the Office of Operations, the Office of Regulatory Affairs, and the other product centers and directorates across the Agency.

4. Will the FDA commit to producing to the Committee a written report of its internal investigation into the root causes and systemic weaknesses that contribute to the lapse related to the unaccountable smallpox vials discovered in July 2014?

Yes. FDA is currently conducting its internal investigation into the root cause and systemic weaknesses that contributed to the lapse related to the unaccountable smallpox vials and other pathogens discovered in July 2014. This investigation is expected to be completed by Fall 2016. Upon the completion of this investigation a final report will be issued, which will be shared with the Committee.

5. Will the FDA commit to issuing a written procedure for the safe transport and securing of select agent materials on-site at FDA or between FDA laboratories, such as when select agents are discovered in locations unregistered with the Federal Select Agent Program?

Yes. FDA is fully committed to ensuring the safety and security of our laboratory scientists and the public. FDA has already issued a Staff Manual Guide (FDA SMG 2130.8) that addresses, among other things, the reporting of select agents and toxins associated with certain discoveries or inventory discrepancies. We are also committed to revising that Staff Manual Guide to include a procedure for the safe and secure transport of select agent materials associated with a discovery or incident. OLSS is working aggressively to ensure that the appropriate policies and protocols are integrated into the SMG for the safe and secure transport of select agent material on-site at FDA and between FDA laboratories when they are discovered in locations unregistered with the Federal Select Agent Program.

If you have further questions, please contact Meghan Scott or Melissa Safford in FDA's Office of Legislation. Meghan may be reached at 301-796-4675 or Meghan.Scott@fda.hhs.gov. Melissa may be reached at 301-796-8914 or Melissa.Safford@fda.hhs.gov.

Thank you for your interest in this matter and your patience in allowing us to respond to your requests. The same letter has been sent to your cosigner.

Sincerely,

A handwritten signature in cursive script, appearing to read "Dayle M. Cristinzio".

for Dayle Cristinzio
Acting Associate Commissioner
for Legislation

cc: The Honorable Frank J. Pallone, Jr., Ranking Member
Committee on Energy and Commerce

The Honorable Diana DeGette, Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30329-4027

September 10, 2016

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your letter requesting information about the current bioterrorism preparedness capabilities of the Centers for Disease Control and Prevention's (CDC) Laboratory Response Network (LRN). The LRN is charged with maintaining an integrated network of state and local public health, federal, military, and international laboratories that can respond to bioterrorism, chemical terrorism, and other public health emergencies.

The LRN is a unique asset in the nation's growing preparedness for biological and chemical terrorism. The linking of state and local public health laboratories, veterinary, agriculture, military, and water- and food-testing laboratories is unprecedented. In the years since its creation, the LRN has played an instrumental role in improving the public health infrastructure by helping to boost laboratory capacity. Laboratories are better equipped, have increased staffing levels, and have employed rapid detection technologies.

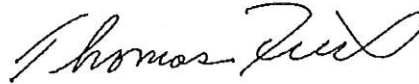
Enclosed please find responses to the specific questions raised in your letter enclosed in two separate documents. Enclosure 1 contains answers to questions 5, 7, and 8. These responses contain non-sensitive information. Enclosure 2 contains answers to questions 1-4, 6, and 9. Because Enclosure 2 contains sensitive information, including information about laboratory capabilities and potential limitations, which may constitute a national security risk if published, we request that Enclosure 2 be kept in a secured location and shared only with those who must review it as part of their official duties, and that the Committee provide CDC an opportunity to redact the document should the Committee plan to release it further, and that the Committee return it to CDC when it is no longer needed.

Thank you for your interest in our efforts to ensure the capabilities of the LRN in protecting the nation's health. We hope this information is helpful to you. If you have any additional questions

Page 2 – The Honorable Fred Upton

or concerns, please have your staff contact Karyn Richman in the CDC Washington Office at (202) 245-0600 or KRichman@cdc.gov. This response is being sent to the cosigners of your letter.

Sincerely,

A handwritten signature in cursive script, appearing to read "Thomas Frieden".

Thomas R. Frieden, MD, MPH
Director, CDC

Enclosures:

1. Responses containing non-sensitive information
2. Responses containing sensitive information

NON-SENSITIVE

Centers for Disease Control and Prevention's (CDC) Responses to the House Committee on Energy and Commerce's Questions regarding Capabilities of the CDC Laboratory Response Network (LRN)

- 5. Please provide a detailed description of the process for qualifying any assay for deployment in the CDC LRN. Please provide details as to what each component or group with CDC or in partnership with other agencies contributes to this effort.**

CDC regularly reviews information on potential biological threat agents and emerging infectious diseases to determine the need for development of diagnostics assays for the LRN. This review considers several factors, including the agent's potential impact on morbidity and mortality; the agent's availability, suitability, and feasibility for use as a biological weapon; the adequacy of current methods for detection and characterization of the agent; availability of medical countermeasures; and evidence suggesting the emergence of an agent as a natural disease threat [e.g., severe acute respiratory syndrome, Middle Eastern respiratory syndrome (MERS), monkeypox, Ebola virus, Zika virus]. Agents are chosen for LRN test development when a test is needed in the public health system based on consideration of these factors.

CDC solicits test development from its internal disease-specific subject matter experts. CDC also works in partnership with the Department of Homeland Security (DHS) to develop assays that meet the sensitivity and specificity requirements of the Public Health Actionable Assay (PHAA) system. When a proposal for a specific assay has been developed, it is submitted to the LRN Program's Design Control Process. This process provides a four-stage review of development and technical readiness of an assay. This process includes reviewers from across CDC and DHS. In addition to filling a gap in preparedness, several other factors are considered in the decision to develop and deploy an assay, including cost of development and sustainability of the assay, ability to manufacture and quality assure the assay, and suitability for LRN's testing platforms.

- 7. Please explain the roles and responsibilities between DHS Science and Technology and CDC relating to the Public Health Actionable Assay Program.**

DHS Science and Technology works in partnership with CDC to develop assays for high-priority threat agents for possible use in the LRN. DHS takes responsibility for developing proof-of-concept assays and performing some evaluation studies with inclusivity and exclusivity organisms that have been identified using PHAA Standards. CDC performs in-depth studies of the assays and determines requirements for acceptable criteria for performance and deployment to LRN laboratories.

8. Does the CDC LRN have the capability to detect emerging infectious diseases (e.g., Zika, MERS, Ebola, novel influenza, chikungunya)? If so, how many CDC LRN laboratories across the nation have such capabilities at the current time? Please provide specific details as to the agent, the type of assay, and the laboratories that have the capability.

The LRN plays a pivotal role in the quick detection of and response to emerging infectious diseases. [REDACTED] LRN Reference laboratories have the capability to detect Zika, dengue, and chikungunya [REDACTED]

[REDACTED] LRN Reference laboratories have the capability to detect MERS [REDACTED]

[REDACTED] LRN Reference laboratories have the capability to rapidly detect *Zaire ebolavirus*. The CDC Influenza Division maintains the capability for testing for novel influenza virus. [REDACTED]

[REDACTED] including state, county, and regional labs, have the capability to test for novel influenza virus. [REDACTED]

[REDACTED]

SENSITIVE

Centers for Disease Control and Prevention's (CDC) Responses to the House Committee on Energy and Commerce's Questions regarding Capabilities of the CDC Laboratory Response Network (LRN)

1. How many CDC Laboratory Response Network (LRN) laboratories are there in the United States? What is their current capability to rapidly detect select agents and toxins?

[REDACTED]

[REDACTED]			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Enclosure 2

2. How many assays have been developed to date to support this critical mission, and when were they developed and deployed?

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3. How many of the select agents and toxins are the CDC LRN laboratories across the nation capable of detecting?

[REDACTED]

[REDACTED]

4. What are the types of assays [REDACTED] developed and deployed by the CDC LRN? Please provide details as to the agent, the type of assays, their limit of detection, etc.

[REDACTED]

[REDACTED]

6. How many assays were developed and deployed through the Public Health Actionable Assay Program in collaboration with the Department of Homeland Security (DHS) Science and Technology Directorate?

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9. Do all of the CDC LRN laboratories have equivalent capacity? If not, please provide the number of laboratories with their specific capability.

Enclosure 2

[REDACTED]
[REDACTED]
[REDACTED] [REDACTED]
[REDACTED]

[REDACTED]



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30329-4027

December 22, 2016

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your follow-up letter requesting additional information about the bioterrorism preparedness capabilities of the Centers for Disease Control and Prevention's (CDC) Laboratory Response Network (LRN).

The LRN is an integrated domestic and international network of laboratories designed to respond quickly to high-priority public health emergency needs through training, rapid testing, timely notification, and secure communication of laboratory results. Through the LRN, CDC—with its partners—develops, maintains, and strengthens our capacity to address a broad range of public health threats, from emerging infectious agents (e.g., Ebola and Zika viruses) to select agents and other potential biological threats.

We have provided, as Enclosure 1, the responses to the questions raised in your letter. Enclosure 1 references tables that list select agents and toxins and indicate which agents and toxins have a material threat determination and whether a corresponding assay (test) has been deployed to LRN laboratories or is maintained at CDC. These tables appear in Enclosure 2.

Enclosure 1 also references several appendices, which are listed in Enclosure 3. Staff from the CDC Washington office is making arrangements with your staff to provide the documents in the appendices.

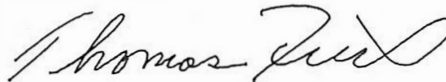
Enclosure 4 is a glossary defining acronyms used in Enclosure 1 and in the appendices.

Because Enclosures 1 and 2 and the appendices contain sensitive information, including detailed information about laboratory capabilities and potential limitations that could compromise national security if published, we request that you keep them in a secured location, share them only with those who must review them as part of their official duties, provide CDC an opportunity to redact the documents should you plan to release them further, and that you return them to CDC when they are no longer needed.

Thank you for your ongoing interest in the capabilities of the LRN to protect the nation's health. We hope this information is useful to you. If you have any additional questions or concerns,

please have your staff contact Barbara Rogers in CDC's Washington office at (202) 245-0600 or BRogers@cdc.gov. This response is also being sent to the cosigner of your letter.

Sincerely,

A handwritten signature in black ink, appearing to read "Thomas Frieden", with a stylized flourish at the end.

Thomas R. Frieden, MD, MPH
Director, CDC

Enclosures:

1. Responses to Questions
2. Tables of Biological Select Agents and Toxins and Their Material Threat Determination, Assay (Test), and Maintenance of Assays at CDC and LRN Labs
3. List of Appendices
4. Glossary of Acronyms

SENSITIVE

The information in this enclosure and referenced appendices is sensitive and should be safeguarded in a manner that protects it from disclosure

Centers for Disease Control and Prevention's (CDC) Responses to the House Committee on Energy and Commerce's Questions in the Committee's Follow-up Letter of October 26, 2016, regarding Capabilities of the CDC Laboratory Response Network (LRN)

1. In response to Question 1, your letter sets out two tables providing current capability information for LRN laboratories to detect select agents and toxins.

a. With regard to the table, "Number of LRN Reference Laboratories Capable of Detecting Select Agents and Toxins,"

[REDACTED]

The U.S. Department of Health and Human Services (HHS)/Centers for Disease Control and Prevention (CDC) and the Department of Homeland Security (DHS) consider different factors in evaluating material under their respective programs. HHS includes biological agents and toxins on the HHS list of biological select agents and toxins (BSATs) if they have the potential to pose a severe threat to human health and therefore warrant security and biosafety measures to prevent their release from laboratories.

In determining whether to include an agent or toxin on the list, the HHS Secretary considers [in accordance with 42 U.S.C. 262a (a)(1)(B)]:

- The effect on human health of exposure to an agent or toxin;
- The degree of contagiousness of the agent or toxin and the methods by which the agent or toxin is transferred to humans;
- The availability and effectiveness of pharmacotherapies and immunizations to treat and prevent illnesses resulting from an agent or toxin; and
- Any other criteria, including the needs of children and other vulnerable populations, that the Secretary considers appropriate.

CDC's Intragovernmental Select Agents and Toxins Technical Advisory Committee considers:

- Organism [its degree of pathogenicity (ability to cause disease) and communicability (ability to spread from infected to susceptible hosts)];
- Production [ease of dissemination, route of exposure, environmental stability (including the ability to retain viable organisms using an aerosol dissemination device), ease of production in the laboratory, and ability to genetically manipulate or alter];

- Host [long-term health effects, acute morbidity (illness), mortality (untreated and treated), available treatment (e.g., medical countermeasures), status of host immunity, vulnerability of special populations, and the burden or impact on the health care system].

[REDACTED]

CDC considers multiple factors in its decision to develop and deploy a test into the Laboratory Response Network (LRN), [REDACTED]

[REDACTED]

CDC also considers the availability of a sufficiently accurate test that can be performed reproducibly across the LRN for all deployed tests for agents and toxins on the HHS BSAT list and for emerging pathogens—such as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Zika virus—that pose a risk of a naturally occurring outbreak in the United States.

[REDACTED]

Development, clearance by the U.S. Food and Drug Administration (FDA), manufacturing, deployment and quality assurance of a laboratory test for a biological agent requires substantial and sustained human, laboratory, and financial resources from CDC, its federal partners, and its state and local laboratory partners [REDACTED]

[REDACTED]

[REDACTED] As good stewards of limited government resources, CDC prioritizes tests based on their ability to have the greatest potential impact. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

b. Are the assays listed in the table, [REDACTED]
[REDACTED]

[REDACTED]

2. In response to Question 2, your letter stated that the LRN developed and deployed a rapid assay for the detection of [REDACTED] [REDACTED] [REDACTED] [REDACTED]. Have any of these assays been fully approved by FDA? [REDACTED]
[REDACTED]
[REDACTED]

Development, manufacture, and deployment of assays for highly infectious or toxic agents is a complex and resource-intensive endeavor. It requires highly specialized laboratory space and

equipment and highly capable and trained scientific staff. [REDACTED]

CDC's steps to develop and improve LRN assays are summarized in Appendix A, "Assay Development Activities, 2003-2016," which provides an overview of agents and assays considered for the LRN since 2003 and identifies the factors considered in approval or rejection of assays. [REDACTED]

[REDACTED] These assays provide information needed to manage more likely bioterrorism attacks or manage outbreaks of emerging infectious diseases, such as MERS-CoV, Ebola virus, or Zika virus. [REDACTED]

CDC has used two pathways for FDA clearance or authorization of laboratory tests for clinical specimens from patients exhibiting signs and symptoms consistent with exposure to chemical and biological agents:

- The 510(k) clearance pathway is a prolonged pathway requiring review of extensive data presented to FDA.
- The Emergency Use Authorization (EUA) pathway permits the FDA to review a laboratory test for authorization in situations, such as an HHS declared public health emergency or a DHS determination of a material threat, where FDA deems the data sufficient to justify the test's use.

3. In response to Question 3, [REDACTED]

As detailed in Appendix A and described above in the answer to question 2, CDC has conducted extensive activities for the development, validation, improvement, deployment, and support of critical diagnostic tests for the LRN. As good stewards of limited government resources, CDC focuses these activities on development and improvements of assays that, if deployed into the LRN, will have the greatest impact in reducing deaths and injuries from a bioterrorist event.

[REDACTED] Appendix A also demonstrates that CDC has devoted considerable effort to development and FDA authorization or clearance of assays for emerging infectious

diseases that pose an imminent threat to the U.S. population. Some of these emerging infectious disease agents, such as MERS-CoV and Zika virus, are not on the HHS BSAT list.

4. In response to Question 5, your letter mentioned several follow-up questions and requests.
- a. Your letter stated that “CDC regularly reviews information on potential biological threat agents and emerging infectious diseases to determine the need for development of diagnostics assays for the LRN.” Based on the reviews CDC has done, what are the agents CDC has determined to have the need for rapid assays?

As mentioned in response to question 3, Appendix A provides a comprehensive overview of tests that CDC has developed or is developing for LRN deployment. CDC is always working to improve tests, particularly those for high-impact agents. CDC is working on multiple improvements to existing rapid tests and on development of new rapid tests, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- b. Your letter further noted evidence suggesting the emergence of an agent as a natural disease threat [e.g., severe acute respiratory syndrome, Middle Eastern respiratory syndrome (MERS), monkey pox, Ebola virus, Zika virus]. Does CDC have FDA-approved assays for each of these agents in the LRN? If not, why not?

[REDACTED]

The table below lists the specific assays and their EUA or 501(k) clearance dates.

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- c. Your letter stated that “[a]gents are chosen for LRN test development when a test is needed in the public health system based on consideration of” several factors. Please provide the assessments and the associated results.

[REDACTED]

[REDACTED]

[REDACTED]

Appendix A, "Assay Development Activities, 2003-2016," lists the assays or improvements that CDC considered for development or deployment into the LRN since 2003, why they were considered priorities, and the outcomes of their evaluations. As of 2016, CDC has used a formal process, called the "Design Control Process" (Appendix B, "LPRB Assay Development and Design Control Review Process Operating Procedure"), when considering development or deployment. The Design Control Process modifies and expands on CDC's earlier Technical Review Committee [Appendix C, "Laboratory Response Network (LRN) Program Office Technical Review Committee (TRC) Charter"], which is no longer in use.

In 2016, CDC also established the Assay Development Working Group (ADW) to formalize the process of evaluating the need for new assays and to ensure participation by key stakeholders. Appendix D, "Centers for Disease Control and Prevention, Division of Preparedness and Emerging Infections (DPEI), Laboratory Preparedness and Response Branch LRN - B Assay Development Workgroup," details the purpose and composition of this group.

From 2013 until the development of the Design Control Process, CDC used a consensus DHS document, "Strategic Implementation Plan for Development, Evaluation, Validation, and Deployment of Public Health Actionable Assays (PHAA)" (Appendix E), in conjunction with the TRC, to prioritize PHAA development, optimization, validation, and deployment efforts between the CDC LRN and DHS Science and Technology. CDC merged this implementation plan with the TRC in 2016 to become the Design Control Process.

- d. Your letter stated that CDC also works in partnership with the Department of Homeland Security (DHS) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

When CDC makes a decision to deploy an assay into the LRN, CDC works with its founding partners (the Association of Public Health Laboratories, the Federal Bureau of Investigation, and the LRN laboratories) to develop a program for training, deployment, and ongoing quality assurance (including proficiency testing).

- e. **Your letter stated that “[w]hen a proposal for a specific assay has been developed, it is submitted to the LRN Program’s Design Control Process.” What is the LRN Program’s Design Control Process? Please provide documentation showing how many assays have gone through the LRN Program’s Design Control Process.**

Appendix B provides the description of the LRN Design Control Process. Appendix C provides the description of the LRN TRC, which preceded the Design Control Process for assay review. Appendix A shows all of the assays that have gone through the TRC and the Design Control Process from approximately 2003 until the present.

- f. **Your letter stated that: “In addition to filling a gap in preparedness, several other factors are considered in the decision to develop and deploy an assay, including cost of development and sustainability of the assay, ability to manufacture and quality assure the assay, and suitability for the LRN’s testing platforms.” Please provide documents for the assessments conducted for each assay and the findings.**

Appendix A, column A lists the assays for which CDC has conducted assessments from 2003 until the present. Column C, Status, lists the associated findings for each assay. Column D indicates why each new assay or improvement was a priority for LRN assay development, a process that takes into consideration a number of factors including [REDACTED]

[REDACTED]

5. In response to Question 6, your letter raises several follow-up questions.

- a. **Your letter stated that assays for detection of [REDACTED] [REDACTED] have been developed in collaboration with DHS, CDC SME’s, and the LRN program according to PHAA standards. When were each of these assays developed? Please provide dates.**
- [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

- b. Your letter stated that assays [REDACTED] have been developed [REDACTED] to PHAA standards and are planned for deployment to the LRN after completion of additional studies. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]

- c. Your letter stated that assays [REDACTED] have been developed [REDACTED] according to PHAA standards [REDACTED] for [REDACTED] consideration for deployment to the LRN. [REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

6. In response to Question 7, your letter stated that “DHS Science and Technology works in partnership with CDC to develop assays for high-priority threat agents for possible use in the LRN.” Please provide the reports provided by DHS to date. Your letter stated that “CDC performs in-depth studies of the assays and determines requirements for acceptable criteria for performance and deployments to LRN laboratories.” Please provide the reports for which CDC has conducted in-depth studies.

Appendices F1-F8 contain reports provided by DHS to CDC and the studies that CDC has performed in follow-up to these reports. Like the CDC documents, the DHS reports are sensitive and should be safeguarded in a manner that protects them from disclosure.

7. In response to Question 8, your letter noted [REDACTED] LRN reference laboratories have the capability to detect Zika, dengue, and chikungunya using a [REDACTED]; [REDACTED] LRN reference laboratories have the capability to detect MERS [REDACTED]; and [REDACTED] LRN reference laboratories have the capability to rapidly detect *Zaire ebolavirus*. Are all of the assays FDA-approved assays? If not, which ones are not FDA approved and why are they not approved? Please provide reports for all of these assays along with documentation associated with the LRN Program’s Design Control Process.
- [REDACTED]
- [REDACTED]
- [REDACTED]

Table A

**U.S. Department of Health and Human (HHS) Services Select Agents and Toxins and Their
Material Threat Determination, Assay (Test), and Maintenance of Assays at CDC and LRN Labs**

[illegible]

Enclosure 2

[illegible]

Enclosure 2

[illegible]

[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Table B

**U.S. Department of Health and Human Services/U.S. Department of Agriculture Select Agents
and Toxins and Their Material Threat Determination, Assay (Test), and Maintenance of Assays at
CDC and LRN Labs**

[illegible]

Enclosure 2

[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]

List of Appendices

Appendix A: Excel Spreadsheet of Assay Development Activities from 2003 to 2016

Appendix B: LPRB Assay Development and Design Control Review Process, effective July 11, 2016, to present

Appendix C: Laboratory Response Network (LRN) Program Office Technical Review Committee (TRC) Charter, effective April 29, 2014, to July 10, 2016

Appendix D: Centers for Disease Control and Prevention/Division of Preparedness and Emerging Infections/Laboratory Preparedness and Response Branch/LRN - B Assay Development Workgroup, effective November 10, 2016 to present

Appendix E: Strategic Implementation Plan for PHAA, effective September 2013 to present

Appendix F: Multiple DHS and CDC reports and studies of certain agents:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Glossary of Acronyms

ADW	Assay Development Workgroup
aLOD	Analytical limit of detection
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
bp	Base pairs
BLAST	Basic Local Alignment Search Tool
[REDACTED]	[REDACTED]
BTRA	Bioterrorism Threat Risk Assessment
CBRN	Chemical, biological, radiological, and nuclear
[REDACTED]	[REDACTED]
CDC	Centers for Disease Control and Prevention
CFU/mL	Colony-forming units per milliliter
[REDACTED]	[REDACTED]
CLIA	Clinical Laboratory Improvement Amendments
Ct	Cycle threshold
%CV	Coefficient of variation
DFWED	Division of Foodborne, Waterborne, and Environmental Diseases
DHF	Design History File
DHS	Department of Homeland Security
DIG ELISA	Diffusion-in-gel enzyme-linked immunosorbent assay
DMR	Device Master Record
DNA	Deoxyribonucleic acid
DoD	Department of Defense
[REDACTED]	[REDACTED]
DPEI	Division of Preparedness and Emerging Infections
[REDACTED]	[REDACTED]
ELISA	Enzyme-linked immunosorbent assay
E-TEST	Epsilometer test, a reagent strip used to determine the minimum inhibitory concentration
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
FERN	Food Emergency Response Network
fg	Femtogram (10 ⁻¹⁵ gram)
[REDACTED]	[REDACTED]
FSAP	Federal Select Agent Program
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
gDNA	Genomic DNA
[REDACTED]	[REDACTED]

Enclosure 4

HHS	U.S. Department of Health and Human Services
HHS BSAT	U.S. Department of Health and Human Services Biological Select Agents and Toxins
IDE	Investigational device exemption
IRB	Institutional Review Board
LANL	Los Alamos National Laboratory
[REDACTED]	[REDACTED]
LOD	Limit of detection
LoQ	Limit of quantification
LPRB	Laboratory Preparedness and Response Branch
LRN	Laboratory Response Network
MAC ELISA	Immunoglobulin M antibody capture enzyme-linked immunosorbent assay
[REDACTED]	[REDACTED]
MCV	Multicenter validation
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MIC	Minimum inhibitory concentration
MS	Mass spectrometry
MTD	Material threat determination
NAT	Nucleic acid test
NCEH	National Center for Environmental Health
NP	Nucleoprotein
nt	Nucleotide
oligos	Oligonucleotides
NTC	No template control
[REDACTED]	[REDACTED]
PCR	Polymerase chain reaction
PDT	Product Development Team
pg	Picogram (10 ⁻¹² gram)
PHAA	Public Health Actionable Assay
PM	Project manager
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
QA/QC	Quality assurance/Quality control
RA	Regulatory affairs
Rapid AST	Rapid antimicrobial susceptibility testing
[REDACTED]	[REDACTED]
rxn	Reaction
TBD	To be determined
TRC	Technical Review Committee
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
SD	Standard deviation
[REDACTED]	[REDACTED]
SME	Subject Matter Expert
spp.	Plural form of "species" (singular form abbreviated as "sp.")

Enclosure 4

██████	████████████████████
Taq	Thermostable DNA polymerase from a thermophilic bacterium, <i>Thermus aquaticus</i>
uL	Microliter
██████	████████████████████
██████	████████████████████
██████	██████
wgs	Whole genome shotgun



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30329-4027

May 23, 2017

The Honorable Greg Walden
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your letter of February 28, 2017, following up on the December 22, 2016, letter from Dr. Thomas Frieden, former director of the Centers for Disease Control and Prevention (CDC), responding to your questions about CDC's Laboratory Response Network (LRN). We appreciate your ongoing interest in the LRN.

The LRN is a critical part of the nation's public health system, defending against biological threats and emerging infectious diseases. The 134 state, local, Department of Defense, and other federal laboratories in the LRN constitute an integrated domestic and international network that responds quickly to high-priority public health emergency needs through training, advanced diagnostics and rapid testing, timely notification, and secure communication of laboratory results. Through the LRN, CDC—with its partners—develops, maintains, and strengthens our capacity to address a broad range of public health threats, from emerging infectious agents to select agents and other potential biological threats. Approximately 85 percent of the U.S. population lives within a two-hour drive of an LRN laboratory, and in the past four years, LRN laboratories have provided Americans with access to critical diagnostic testing for Ebola and Zika viruses.

We have provided, as Enclosure 1 and its associated appendices, detailed responses to each of the requests and questions in your letter. Enclosure 2 is a list of the appendices.

Because Appendices I A and B, II, and VII, which correspond to responses to questions 1, 5, and 9, contain sensitive information, including detailed information about laboratory capabilities and potential limitations that could compromise national security if published, we request that you keep them in a secured location, share them only with those who must review them as part of their official duties, provide CDC an opportunity to redact the documents should you plan to release them further, and return them to CDC when they are no longer needed.

Thank you for your letter and your interest in protecting the nation's health. This response is

Page 2 -- The Honorable Greg Walden

also being sent to Representative Tim Murphy.

Sincerely,

A handwritten signature in cursive script, appearing to read "Anne Schuchat", with a long horizontal flourish extending to the right.

Anne Schuchat, MD
(RADM, U.S. Public Health Service)
Acting Director, CDC

Enclosures

Centers for Disease Control and Prevention's (CDC) Responses to Questions in the House Committee on Energy and Commerce's Follow-up Letter of February 28, 2017, regarding Capabilities of CDC's Laboratory Response Network (LRN)

1. A table delineating the following information: name of each federal select agent, tests developed for detecting each federal select agent, names of LRN labs that have each test, dates of when each of these tests were deployed to the LRN labs, and for each test indicate whether the test was evaluated and validated by CDC as described in the December 22, 2016, letter.

Appendix I contains two tables with the requested information. Table A, LRN Assays Available for Select Agents and Toxins, lists the tests developed for each select agent or toxin and dates of deployment to LRN laboratories, and indicates whether tests have been evaluated or validated by CDC.

Table B, LRN Lab Capacity for Each Test, lists the LRN facilities able to test for each select agent or toxin.

Tables A and B are sensitive and should be handled in a manner that protects them from disclosure.

2. For each of the last 15 fiscal years, provide the level of funding from the budget of the CDC Division of Preparedness and Emerging Infections that was allocated to support the LRN.
 - a. For each of the last 15 fiscal years, how much was spent to maintain LRN reagents?
 - b. For each of the last 15 fiscal years, how much was spent on research and development efforts on assays for the LRN?
 - c. For each of the last 15 years, how much was spent on the hiring staff to support the LRN activities, and how many staff were hired to support LRN activities? Of the additional staff hired, how many worked full-time to support LRN activities? How many worked part-time to support LRN activities?

Table 1, below, provides the requested information on all LRN-related activities conducted by the CDC Division of Preparedness and Emerging Infections (DPEI) from fiscal year (FY) 2007-2016. CDC does not receive appropriations designated for the LRN, and information prior to FY 2007 is not available. The information in Table 1 includes CDC appropriations and funding from other federal agencies.

Table 1. LRN Expenditures, 2007 – 2016

Fiscal Year	LRN Total Annual CDC Expenditures ¹	LRN Reagent Expenditures	Research and Development Expenditures	Personnel Support	
2007	\$9,107,709	\$2,962,316	\$762,751	\$2,214,769	
2008	\$8,711,562	\$1,662,560	\$841,638	\$2,637,461	
2009	\$8,141,717	\$1,029,026	\$543,708	\$2,957,723	
2010	\$7,637,661	\$729,200	\$623,730	\$2,637,682	
2011	\$7,853,388	\$563,400	\$560,318	\$2,877,682	
2012	\$6,692,774	\$579,080	\$632,436	\$3,074,915	
2013	\$6,820,819	\$619,100	\$537,983	\$3,372,260	
2014	\$6,320,133	\$475,050	\$550,075	\$3,172,260	
2015	\$5,781,436	\$367,596	\$574,773	\$3,053,399	
2016	\$5,420,670	\$466,455	\$405,875	\$2,796,670	

¹ The “LRN Total Annual CDC Expenditures” column includes total LRN expenses for each fiscal year, including contracts and supplies, which are not included in the LRN Reagent, Research and Development, or Personnel columns.

[REDACTED]

3. For each of the last 15 fiscal years, how much funding has been provided to CDC by the Department of Homeland Security and any other federal agencies to support LRN activities?

CDC receives funding for multiple activities from the Department of Homeland Security (DHS) Table 2 summarizes funding provided to CDC from the DHS/Science and Technology Directorate to support LRN activities across CDC. Because of the variety of activities included and the mechanisms used to transfer and allocate these funds, this table may not be complete.

Tables 3, 4, and 5 summarize funding provided in support of LRN activities from the Department of Defense (DoD)/Defense Threat Reduction Agency (DTRA), the Department of Health and Human Services (HHS)/Office of the Assistant Secretary for Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA), and the DoD/Joint Program Executive Office (JPEO), respectively.

CDC has information on funding from these agencies from FY 2008 to the present.

Table 2. Funds Provided from DHS/Science and Technology Directorate to Support LRN Activities across CDC

Fiscal Year*	Funding
2008	\$267,000
2009	\$4,597,816

2010	\$1,818,239
2011	\$1,320,460
2012	-
2013	-
2014	-
2015	\$1,180,000
2016	-

** CDC does not track LRN-designated funding separately from other DHS funded activities. This table may not be complete.*

Table 3. Funds Provided from DoD/DTRA to Support LRN Activities

Fiscal Year*	Funding
2012	\$3,596,000
2013	\$2,011,000
2014	-
2015	-
2016	\$491,149

** No funding between FY 2008-2011, or in FY 2014-2015*

Table 4. Funds Provided from HHS/ASPR/BARDA to Support LRN Activities

Fiscal Year*	Funding
2013	\$2,717,301
2014	\$1,839,455
2015	\$1,800,000
2016	-

** No funding between FY 2008-2012, or in FY 2016*

Table 5. Funds Provided from DoD/JPEO to Support LRN Activities

Fiscal Year*	Funding
2015	\$49,000
2016	\$40,171

** No funding between FY 2008-2014*

4. Please provide a list of assays developed for the LRN by CDC that have been submitted to the U.S. Food and Drug Administration (FDA) for 510(k) clearance, the dates of submission, and the status.

CDC has used two pathways for FDA clearance or authorization of laboratory tests for clinical specimens from patients exhibiting signs and symptoms consistent with exposure to chemical and biological agents:

- o The 510(k) clearance pathway is a prolonged pathway requiring review of extensive data presented to FDA.
- o The Emergency Use Authorization (EUA) pathway permits the FDA to authorize the emergency use or distribution of investigational products, or unapproved uses of approved products in certain situations, such as after the Secretary of HHS has determined that there is a public health emergency or significant threat of a public health emergency or after the Secretary of DHS has identified a material threat sufficient to affect the national security or the health and security of U.S. citizens living abroad, and the Secretary of HHS has declared that circumstances exist to justify the authorization of the emergency use of the product.

5. CDC's December 22, 2016, letter stated, "As good stewards of limited government resources, CDC prioritizes tests based on their ability to have the greatest potential

impact.” Which tests is CDC referring to? How does CDC make such a determination? What are the criteria? Please provide any documents in support of this statement.

The sentence quoted above from the CDC’s December 22, 2016, letter refers to laboratory tests selected for development in the LRN. The LRN provides testing for early detection and characterization of potential biological terrorism agents and emerging infections. It prioritizes tests based on the potential impact of the agents on the U.S. population and the potential for mitigation of this impact through early detection and characterization. CDC uses a standard approach for assessment of the potential impact of potential biological terrorism agents which CDC published in 2002. [Rotz LD, *et al.* (2002). Public health assessment of potential biological terrorism agents. *Emerging Infectious Diseases*; 8(2): 225-230. Available at wwwnc.cdc.gov/eid/article/8/2/01-0164_article.] This approach uses several criteria to evaluate potential bioterrorism agents, including public health impact, dissemination potential, public perception, and difficulty of obtaining and preparing a weaponized form of the agent. CDC also uses DHS’s Threat Risk Assessments, which incorporate assessments from multiple intelligence agencies. Although the Threat Risk Assessments are classified, the process of creating and improving them is described in the following publically available sources:

- Testimony of Chief Medical and Science Advisor Segaran Pillai, Ph.D., Science and Technology Directorate Chemical and Biological Defense Division [of DHS], before the U.S. House Committee on Homeland Security, Subcommittee on Emergency Preparedness, Response, and Communications, "Taking Measure of Countermeasures (Part 1)." Available at www.dhs.gov/news/2011/04/14/written-testimony-st-house-homeland-security-subcommittee-emergency-preparedness.
- Parnell GS *et al.* (2008). Scientists Urge DHS to Improve Bioterrorism Risk Assessment. *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*; 6(4): 356-356. Available at <http://online.liebertpub.com/doi/pdf/10.1089/bsp.2008.0930>.

Because the mission of the LRN includes the early detection and characterization of emerging infectious diseases, CDC also assesses the potential impact of newly emerging infections and the need for LRN testing. CDC uses international surveillance for emerging infections and the opinions of international and CDC subject matter experts to guide prioritization of tests for development of LRN tests. When the Ebola epidemic emerged in West Africa in 2014, CDC arranged for the evaluation and deployment of a DoD Ebola Zaire assay into the LRN. CDC began development of an LRN diagnostic for Zika virus shortly after recognition of the Zika epidemic in Brazil in 2015.

Recently, CDC charged the Assay Development Working Group with formally prioritizing assays for future development. Please see the LRN-B Development Workgroup Charter, attached as Appendix II. *This document is sensitive and should be handled in a manner that protects it from disclosure.*

6. [REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]			
[REDACTED]	[REDACTED]		
	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

7. [REDACTED]

[REDACTED]

8. With regard to CDC's development of a rapid, highly sensitive assay that can be performed on a commercially available, [REDACTED] platform, CDC's December, 22, 2016, letter stated that this assay "is entering the third of six phases of development" of the Laboratory Assay Development and Design Control Review Process Operating Procedure before submission to the FDA for 510(k) clearance and deployment into the LRN." Please provide the details about each of the six phases. Have all assays developed by CDC for the LRN undergone the six-phase process? If not, why not?

The Laboratory Assay Development and Design Control Review Process Operating Procedure is intended to ensure that new and existing products (regulated and non-regulated) meet user needs, intended uses, and specified requirements to support the LRN. Each of the six phases of the process is described in *LPRB Assay Development and Design Control Review Process Operating Procedure*, attached as Appendix V. Table 8, below, summarizes the six phases.

Table 8. Summary of the Six Phases of the Laboratory Assay Development and Design Control Review Process

Phase	Objective(s)
Phase 1: Concept Approval	<ul style="list-style-type: none"> a) To evaluate proof-of-concept for an assay/product. b) To determine appropriateness of proceeding with development considering the resulting benefit and available resources.
Phase 2: Design Plan and Input	<ul style="list-style-type: none"> a) To develop assay/product requirements based on established need(s); requirements are documented as "inputs" that can be validated as "outputs" in subsequent phases. b) To develop a strategy, process, and timeline for how the assay/product requirements will be accomplished.
Phase 3: Analytical Verification	To evaluate the analytical performance of the product. Data generated will provide information related but not limited to sensitivity, specificity, accuracy, repeatability, linearity, etc.
Phase 4: Design Validation	<p>To confirm that the product conforms to defined user needs and intended uses when tested under actual or simulated use conditions.</p> <p>Validation is performed on product manufactured under good manufacturing practices-like conditions and tested in a customer environment for its intended use. All applicable internal, external, and clinical trials and validation testing are completed.</p>

Phase 5: Design Transfer	To formally transfer the assay/product design to manufacturing and training of manufacturing personnel.
Phase 6: Distribution	The assay/product is considered approved for distribution to designated laboratories.

CDC implemented the Laboratory Preparedness and Response Branch (LPRB) Design Control Process in July 2016 to replace the previous process, known as the Technical Review Committee (TRC) Process, which has since been discontinued. Assays that were completed from October 2003 through July 2016 were approved through the TRC process. Assays in development were transitioned to the LPRB Design Control Process, starting from Phase 1. Appendix VI, "Assay Development Activities," shows the assays that were completed under the TRC, as well as the assays that were transitioned from TRC to LPRB Design Control and are ongoing.

9. CDC's December 22, 2016, letter stated that CDC established the Assay Development Working Group in 2016. Please provide the names of the members and their agencies. Has the Working Group met? If so, when? What was the outcome of the meeting(s)?

The names and affiliations of the members of the Assay Development Working Group are listed in Appendix VII. *This document is sensitive and should be handled in a manner that protects it from disclosure.*

Below are summaries of the two meetings of the Assay Development Working Group, which met on December 9, 2016, and on February 24, 2017:

- During the December 9, 2016, meeting, the chairperson made introductions and explained the mission of the working group. The charter was reviewed and discussed, and minor clarifications were made. The chairperson provided an overview of the LPRB Design Control Process for development of assays for use in the LRN and then outlined the assays currently under development at CDC.
- During the February 24, 2017, meeting, action items from the previous meeting were discussed. The process for prioritizing agents for assay development was discussed. A list of agent prioritization criteria was created for the group to discuss and deliberate. Once elements are finalized, the criteria will be ranked by the workgroup.

List of Appendices

Appendices I, II, and VII contain sensitive information and should be safeguarded in a manner that protects them from disclosure.

Appendix I (question 1):

- **Table A:** LRN Assays Available for Select Agents and Toxins
- **Table B:** LRN Lab Capacity for Each Test

Appendix II (question 5): LRN -- B Assay Development Workgroup Charter

Appendix III (question 6): [REDACTED]

Appendix IV (question 7): [REDACTED]

Appendix V (question 8): LPRB Assay Development and Design Control Review Process Operating Procedure

Appendix VI (question 8): Assay Development Activities 2003 – 2016

Appendix VII (question 9): Members of Assay Development Working Group

Report in Brief

Date: June 2017

Report No. A-04-16-03554

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
OFFICE OF INSPECTOR GENERAL



Why OIG Did This Review

Created in 1999, the Strategic National Stockpile (Stockpile) is a repository of vaccines, antibiotics, antidotes, antitoxins, medications, and supplies, in addition to certain controlled substances, meant to supplement and resupply State and local public health agencies in the event of a national emergency.

Previous OIG audits in 2005 found that Stockpile sites lacked adequate protection against theft, tampering, destruction, or other loss. Although our recent audits of five selected Stockpile sites confirmed that Stockpile inventory was adequately protected, we identified some issues within the Stockpile inventory system. This report summarizes those five audit reports and describes issues we identified as risks to the Stockpile if the Centers for Disease Control and Prevention (CDC) does not take corrective action.

The objective of our review was to identify systemic issues that could prevent CDC from ensuring that Stockpile sites are adequately protected and inventory is readily deployable in a public health emergency.

How OIG Did This Review

For this report, we reviewed the findings from each of five Stockpile site audits that covered FYs 2013 and 2014. We also reviewed additional information related to the value of the Stockpile, as well as Stockpile security and funding.

Readiness of CDC's Strategic National Stockpile Could Be at Risk in Case of a Public Health Emergency

What OIG Found

Two primary systemic issues may prevent CDC from ensuring that Stockpile sites are adequately protected and that inventory is readily deployable in a public health emergency:

- although no longer responsible for providing Stockpile security, the Division of Strategic National Stockpile (DSNS) still controls security funding and
- the Stockpile automated inventory system did not always accurately track the movement of all inventory or accurately record inventory locations.

DSNS controls funding for Stockpile security because, in 2005, CDC transferred responsibility for physical security protection of the Stockpile from DSNS to its Office of Safety, Security, and Asset Management (OSSAM) but did not transfer security funding to OSSAM. The automated inventory system did not always accurately manage Stockpile inventory because DSNS has not taken steps to ensure that the system has the necessary capabilities to do so. These systemic issues could place at risk approximately \$7 billion of Stockpile inventory and negatively affect Stockpile readiness during a national emergency.

What OIG Recommends and CDC Comments

We recommend that CDC (1) consider directly funding OSSAM's Stockpile security mission and (2) improve its automated inventory system so that it can accurately identify inventory movements and locations at all times.

CDC concurred with our recommendations and described steps that it had taken or planned to take to address our recommendations.

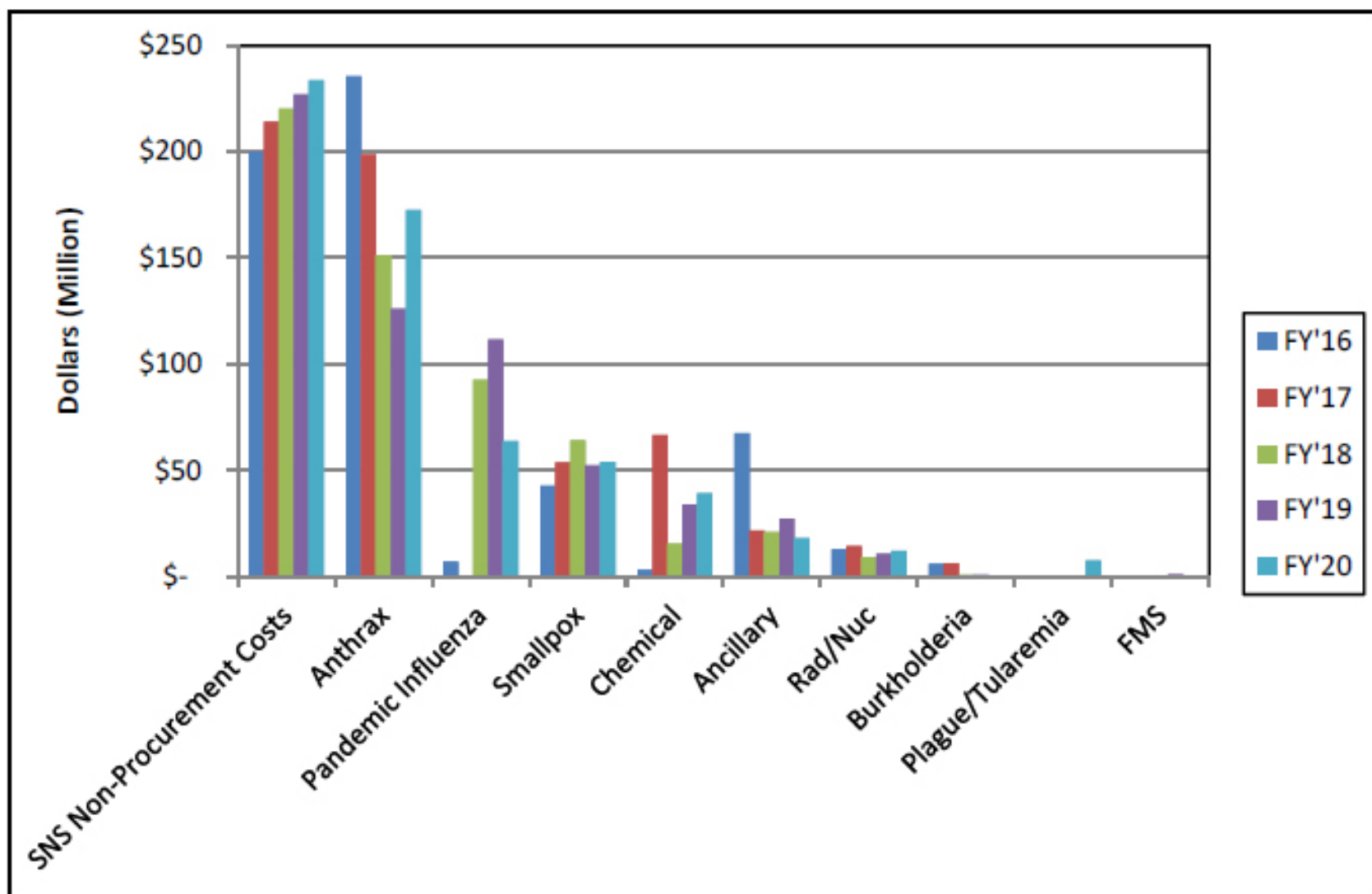


Figure 5: Estimated DSNS Spending, by Portfolio