"Examining the Reauthorization of the Pandemic All-Hazards Preparedness Act"

Statement of
M. Michelle Berrey, MD, MPH
President and Chief Executive Officer
Chimerix, Inc.
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Introduction

I would like to thank Chairman Burgess, Ranking Member Green, and all members of the Committee for the opportunity to speak to you today in support of the reauthorization of the Pandemic and All Hazards Preparedness Act (PAHPA).

I am an Infectious Disease and Public Health physician by training. I have spent most of the last 20 years developing new drugs for viral diseases. I currently serve as CEO of Chimerix, a small biopharmaceutical company of 85 employees that is headquartered in Durham, North Carolina. Our lead product candidate, brincidofovir, is an antiviral with activity against many different viruses. This compound is in the late stages of development for the treatment of smallpox and is in concurrent development for the treatment of patients with life-threatening adenovirus infections, making it one of only a handful of "dual-use" agents.

In addition to supporting the proposed reauthorization of PAHPA, I aim to highlight the important components of a successful public-private partnership that supports the discovery and development of needed medical countermeasures.

We at Chimerix are fortunate to have received government funding to jumpstart our smallpox development program. In 2003, a grant from the U.S. National Institute of Asthma

and Infectious Diseases (NIAID) allowed us to begin research on brincidofovir for the treatment of smallpox infections and complications resulting from smallpox vaccination. By 2011, this collaboration with NIAID had enabled us to complete the early development work and we subsequently initiated a new partnership with the U.S. Biomedical Advanced Research and Development Authority (BARDA). The goal of our continuing work with BARDA is to develop brincidofovir as a medical countermeasure against smallpox.

Vaccination is intended to be the first line of defense in the event of a smallpox release. BARDA's Smallpox Vaccine Program has a stated goal of having enough smallpox vaccine for the entire Nation. This includes a vaccine for the general population, and an attenuated vaccine for the estimated 20% of Americans who may not be able receive the live virus vaccine, including those who may be pregnant, individuals living with HIV, or the three million Americans currently taking a biologic for autoimmune or other diseases.[1]

The Institute of Medicine recommends that, in addition to vaccines, the U.S. stockpile two different smallpox antivirals with different mechanisms of action. These would serve to treat those who remain ineligible for a vaccine and to treat individuals with symptomatic smallpox.

Biological Weapons Pose a Serious and Growing Threat to the United States

Unfortunately, the threat of a biological weapon impacting the United States has never been more real. This year marks the 100th anniversary of the Spanish Flu, which killed an estimated 50-100 million people worldwide. In today's interconnected world, it is difficult to overestimate the devastation that a highly infectious agent—whether natural or manmade—would wreak. Of note, smallpox, like influenza, is transmitted through

[1] MacIntyre C, Costantino V, Chen X, Segelov E, Chughtai A, Kelleher A, et al. Influence of Population Immunosuppression and Past Vaccination on Smallpox Reemergence. Emerg Infect Dis. 2018;24(4):646-653. https://dx.doi.org/10.3201/eid2404.171233

respiratory droplets and does not require contact with bodily fluids. In fact, smallpox is two to three times more infectious than the flu virus.[2]

Several weeks ago, the Johns Hopkins Center for Health Security conducted a tabletop exercise simulating the spread of a novel virus across the globe. In their simulation, the failure to develop a vaccine within 20 months led to 150 million deaths globally.[3] Health care systems collapsed, the U.S. stock market crashed, and the American political system was in upheaval.[4] Exercises like these highlight the importance of PAHPA and the public-private partnership to stockpile medical countermeasures and build the expertise needed to protect our country.

The U.S. stopped vaccinating routinely against smallpox in 1971, as progress was being made toward the eradication of smallpox. The only labs in the world approved to have the virus for research are in the U.S. and Russia.[5] For many years, national security and health experts debated the merits of eradicating these existing stockpiles. Unfortunately, recent scientific research and publications have rendered that debate moot.

In January of this year, a team of Canadian researchers published in an online open-source journal their methodology for recreating the horsepox virus from materials ordered from scientific catalogs. As suggested by the name, horsepox is closely related to both cowpox and smallpox. This confirms that standard scientific methods could be utilized to synthetically create smallpox *de novo*. This new synthetic smallpox could be altered slightly to have a higher mortality rate than the estimated 30% of naturally-occurring smallpox from *Variola major* (last reported in 1975[6]), or to be resistant to currently stockpiled vaccines or antivirals. Perhaps even more concerning, the project cost only about $100,000 and took a small team about six months.[7] This is not only achievable for

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[2] Gani R, Leach S., "Transmission potential of smallpox in contemporary populations." Nature. 2001 Dec 13;414(6865):748-51.
[3] Lena Sun, "This mock pandemic killed 150 million people. Next time it might not be a drill.," Wash. Post, May 30, 2018.
[4] *Id.*
[5] CDC, "Bioterrorism: Smallpox," https://www.cdc.gov/smallpox/bioterrorism/public/threat.html (Dec. 19, 2016).
[6] *Id.*
[7] Noyce RS, Lederman S, Evans DH, "Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments." PLOS ONE (Jan. 19, 2018), *available at* https://doi.org/10.1371/journal.pone.0188453

state actors like North Korea—which may already have a stockpile of smallpox—but for highly motivated rogue actors.

If weaponized, smallpox could be devastating. Since this virus is most commonly transmitted person-to-person via respiratory droplets, a single sneeze or cough could release thousands of viruses into the air where they could be inhaled or land on mucous membranes in the eye, nose, or throat. Smallpox has an initial prodromal period, very much like Ebola, during which the individual has no symptoms and is not infectious.[8] By the time someone begins to have a fever and rash—a time when they would be very infectious—and presents at an emergency room or clinic, they could have spread this virus to their immediate family, to those on public transportation, or to other patients in an ER waiting room. Compounding the problem, very few physicians practicing in emergency rooms today have ever seen smallpox, or would think to test a patient with a new rash for smallpox. Consequently, it would be very difficult to trace smallpox infections and the disease could rapidly spread across the globe.[9]

Importantly, brincidofovir meets all U.S. Government requirements for a second antiviral for the SNS:

- Dosed orally, with a short course of therapy;
- Clinical experience in more than 1,500 patients, including relevant populations of immunocompromised patients through our adenovirus and cytomegalovirus research programs, and importantly, clinical safety and efficacy data for other viruses in pediatric patients;
- High barrier to resistance;
- Strong efficacy in animal models, meeting the FDA's criteria of "reasonably likely to predict benefit in humans"; and
- A development path to approval agreed upon with the FDA.

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[8] WHO, "Smallpox," http://www.who.int/biologicals/vaccines/smallpox/en/ (Jan. 14, 2014).
[9] *Id.*

We are committed to completing the development program for brincidofovir as quickly as possible so we are able to offer a much-needed second treatment option for smallpox to the SNS.

Brincidofovir Development Program

To date, we have completed over a dozen efficacy studies of brincidofovir for the treatment of smallpox under the FDA's Animal Rule. This rule allows for efficacy testing in animal models in diseases that are not ethical or feasible to study in humans. Because smallpox was successfully eradicated, there is no existing population of patients for testing.

We are proud of the progress we have made in the brincidofovir development program in smallpox, demonstrating improved survival rates following confirmed orthopoxvirus infections in multiple animal models. Our studies also show that brincidofovir may reduce transmission of smallpox by accelerating clearance of virus. This component could be critical in stopping an outbreak.

Chimerix recently reached agreement with the FDA for a general study design for a final rabbitpox study, which will be conducted in parallel with a registrational mouse study this year. We anticipate that results will be available in early 2019 for both studies. Chimerix plans to submit regulatory applications in both the U.S. and Europe for approval of brincidofovir for smallpox in 2020.

Conducting studies to determine a medicine's efficacy under the Animal Rule is complex and provides a less-than-straight path to approval. Establishing rigorous animal models requires a great deal of planning, analysis, and ultimately, trial and error. These efforts demand significant resources and investment. Reauthorizing PAHPA ensures that there is dedicated funding ahead for stockpiling this is critical as there is no existing commercial marketplace for an antiviral for smallpox. We are developing a solution for a problem that we all hope never presents itself, but *not* being prepared for a smallpox event is *not* an option.

Brincidofovir is also in clinical development for emerging life-threatening viral diseases in patients that do not have an intact immune system, making it a "dual use" compound. We are currently pursuing what would be our first commercial indication for the treatment of adenovirus in pediatric stem cell transplant recipients.

As a small, clinical-stage company focused on transforming survival rates in these pediatric patients, we face specific challenges in advancing both commercial and government research programs for brincidofovir in adenovirus and smallpox, respectively. For example, the safety and tolerability of the compound in different populations is important to understand. We would recommend that additional guidance be provided within the current Animal Rule for dual-use compounds such as ours.

Because a majority of the adenovirus patient population are children, we have optimized an oral suspension that does not require refrigeration, an important characteristic for medicines in the SNS. Independent of our BARDA collaboration, we also identified the need for an intravenous (IV) formulation for hospitalized patients with active viral infection who may not be able to be treated with an oral medicine. BARDA has expressed interest in exploring the utility of the IV formulation of brincidofovir for potential utility in patients with active smallpox infection. Thus, the dual-use development of brincidofovir maximizes the application of federal monies and taps into the recognized innovation of the American biotechnology sector.

Lessons Learned From Partnership With BARDA

Our private-public partnerships over the last seven years, particularly with BARDA, have been critical to the survival and progression of our smallpox program. BARDA's leadership and staff are committed to improving our nation's preparedness for a biological attack, and we are deeply appreciative of their service and grateful for the opportunity to serve as private-sector partners. Our experience has underscored the importance of ongoing and

transparent communication between companies and government organizations engaged in biodefense research. The unpredictable nature of government funding, however, makes it challenging to maintain momentum. Without a guaranteed government marketplace, capital to maintain the necessary research and development programs is difficult to secure.

Reauthorizing PAHPA Is Critical for Our Nation's Preparedness

With its passage twelve years ago, PAHPA created a series of public-private partnerships that have been remarkably successful. The passage of the Project BioShield Act and then PAHPA created a market for medical countermeasures for the first time. This provided the incentive for companies like ours to take the risk of partnering with the government and devoting substantial time and resources to developing these therapies.

Mass media outlets sometimes give the false impression that if a novel biological threat reaches the U.S., scientists would quickly be able to develop and deploy a countermeasure. The reality is that science takes time. Our company is a prime example of the fact that researching and developing a medical countermeasure takes years of sustained investment. Another recent example is Siga Technologies' development path, from its founding in 1995 to the FDA approval for its smallpox antiviral which is expected later this year.

In BARDA's objectives, the agency has specified stockpiling two different antivirals in the SNS with activity for smallpox. This is not only important in the case of viral resistance, but potentially, as a form of combination therapy. As we have seen in other infectious diseases, combination therapy, or "cocktails," can be much more effective than a single drug, and this could potentially be an option when treating an active smallpox infection.

Stockpiling of medical countermeasures is critical because manufacturing sufficient quantities of product to reach affected populations cannot happen overnight. By facilitating product development and stockpiling quantities of medical countermeasures, Project BioShield and PAHPA provide a critical bulwark against potential biological threats.

The impact of these programs has been undeniable. According to ASPR, since the passage of PAHPA, 34 medical countermeasures have been approved or licensed by the FDA and 14 have been placed in the SNS. Twenty-seven medical countermeasures are currently supported by Project BioShield, and more than 200 candidates are in the development pipeline. Moreover, PAHPA has created a community of scientists, academics, and policymakers focused on cross-collaboration and preparedness. This network will be vitally important if and when the U.S. is faced with a biological threat.

We commend the Committee for the bipartisan collaboration on the PAPHPA reauthorization. In particular, we appreciate inclusion of the ten-year advance appropriation for the Project BioShield Special Reserve Fund. Companies like ours rely on the existence of a government market for medical countermeasures to sustain the long-term investment in researching and development of these therapies. Under the annual appropriations process we have had in place in recent years, this government market guarantee has become uncertain.

In fact, a recent report by the Bipartisan Policy Center found that since Project BioShield reverted from its original ten-year advance appropriation to annual appropriations, the dollar value and scope of awards have been significantly reduced, creating uncertainty for the private sector and raising questions about the sustainability of the medical countermeasure enterprise.[10] Returning to a ten-year advance appropriation would provide increased certainty that will allow emerging companies like ours to continue this partnership and hopefully, encourage other innovative companies to enter this space.

Conclusion

We are proud of our partnership with BARDA and our role in contributing to the United States' preparedness for a biological attack. We encourage the Committee to reauthorize

[10] Bipartisan Policy Center, Budgeting for Medical Countermeasures: An Ongoing Need for Preparedness 4, 9 (Feb. 2018).

PAHPA and build on the successes of the past twelve years to help sustain this vital public-private partnership for the years ahead.