

Questions for the Record

House Energy and Commerce Committee, Subcommittee on Health

Nov. 19, 2014, Hearing: “Examining Medical Product Development in the Wake of the Ebola Epidemic”

Dr. Anthony Fauci, Director, NIAID

NOTE: CONTENT ACCURATE AS OF JANUARY 20, 2015

The Honorable Joseph R. Pitts

1. As you know, there is an important public-private partnership that takes place between NIH/NIAID and the private sector with ongoing Ebola vaccine and drug research, as well as MCMs against other threats.
 - a. Please describe the importance of this partnership.
 - b. Please describe how the research at NIAID eventually moves to advanced development projects at BARDA?
 - c. Would you say this process has been successful? How could it be improved?

NIAID Response: Partnerships with industry are critical in NIAID’s efforts to develop therapeutic and vaccine candidates for Ebola and other emerging and re-emerging infectious diseases. In this endeavor, it is important to have as many vaccine and therapeutic candidates as possible because candidates that showed early promise may not proceed successfully through the entire development pipeline. To this end, NIAID collaborates with the private sector, including small businesses, academic researchers, and biotechnology and pharmaceutical companies, to identify, develop, and evaluate promising medical countermeasures (MCMs).

For example, partnerships between NIAID and industry have facilitated the Phase I clinical testing of Ebola vaccine candidates. NIAID advanced one of these candidates, cAd3, in partnership with the pharmaceutical company GlaxoSmithKline (GSK). NIAID is conducting Phase I trials of this candidate and an additional vaccine candidate, rVSV-EBOV, developed by the Public Health Agency of Canada and licensed to NewLink Genetics Corp. In collaboration with GSK, the Department of Defense (DOD), the Government of Liberia, and NewLink, plans are underway to move these vaccine candidates into Phase II/III efficacy testing, including in West Africa.

In addition to Ebola vaccine candidates currently in clinical trials, NIAID has partnered with universities and biotechnology and pharmaceutical companies to support a number of Ebola virus vaccine candidates in various stages of development. NIAID also supports research on MCMs by providing preclinical services such as animal testing to researchers. These resources are designed to assist academic and industry partners in advancing their products along the development pipeline. For example, NIAID’s preclinical services have been used by private

partners to evaluate more than 30 different filovirus vaccine formulations since 2011. Several of these candidates qualified for further testing, and a number are currently undergoing further development by private industry; Johnson & Johnson recently began a Phase I trial of an Ebola vaccine candidate developed with NIAID preclinical services and direct support.

In the development of all MCMs for biodefense and emerging and re-emerging infectious diseases, NIAID coordinates with multiple partners to translate scientific discoveries into safe and effective MCMs. If candidate MCMs show promise in animal studies or early human testing, NIAID transitions these candidates to the Biomedical Advanced Research and Development Authority (BARDA) for advanced development. This process has worked well to advance development of a number of important MCMs; examples of recent successful transitions from NIAID to BARDA include vaccines and therapies for anthrax, smallpox, and pandemic influenza, including two smallpox antiviral drugs, and a next-generation treatment for chemical exposure. NIAID works closely with BARDA to continually assess the transition process and incorporate lessons learned from previous successful transitions.

In partnership with BARDA and others, NIAID is working to accelerate the development of MCMs for Ebola virus to respond to the current outbreak in West Africa. NIAID is partnering with DOD and BARDA to advance the development and testing of the Ebola therapeutic candidate ZMapp. ZMapp, developed by Mapp Biopharmaceutical, Inc., with support from NIAID and DOD, is a combination of three antibodies that has been shown to protect monkeys from death due to Ebola virus. NIAID's preclinical services are being used to provide preliminary safety data to support the use of ZMapp for clinical trials in humans. BARDA is working with Mapp Biopharmaceutical to accelerate the manufacturing of more ZMapp so that clinical safety and efficacy testing can begin as soon as possible. BARDA is supporting the large scale production of the NIAID/GSK and NewLink Ebola vaccine candidates for potential mass vaccination campaigns.

NIAID's longstanding and successful collaborations with BARDA and other partners are critical to the development of treatments and vaccines for Ebola virus disease. As additional MCMs show promise in early-stage testing, NIAID will continue to coordinate closely with BARDA to transition these candidates for advanced development.

- 2. Please provide the Committee with an overview of the Ebola vaccine candidates that are on the horizon and where they are in the process of moving into clinical trials and eventual mass vaccination campaigns in West Africa. As I understand it, your Institute has been funding the development of not only a monovalent Ebola vaccine, but also a multivalent Ebola/Marburg vaccine.**

NIAID Response: A safe and effective Ebola vaccine could be a critically important tool to help prevent Ebola virus disease and help contain future outbreaks. The hope is that such a vaccine could be licensed and used in the field to protect frontline healthcare workers and individuals living in areas where Ebola viruses exist. NIAID has worked to advance a number of Ebola

vaccine candidates into clinical testing to determine if they are safe and effective in preventing Ebola virus disease.

NIAID is currently testing or collaborating with partners to test Ebola vaccine candidates in Phase I/Ib clinical trials in the United States, Europe, and Africa, with plans to move promising candidates into Phase II/III efficacy testing, including in West Africa. NIAID, in partnership with GlaxoSmithKline (GSK), developed two versions of the chimp adenovirus-vectored cAd3 Ebola vaccine. The first is a bivalent cAd3 vaccine that contains genes from two Ebola virus species, including the Zaire Ebola virus responsible for the current outbreak in West Africa. A small Phase I study to examine the safety and ability of this candidate to induce an immune response in humans began on September 2, 2014, at the NIH Clinical Center in Bethesda, Maryland. Initial results from this trial indicated the vaccine is well-tolerated and produced immune system responses in all 20 healthy adults who received it. The second version of the cAd3 vaccine is a monovalent vaccine including just a single Zaire Ebola virus gene. The monovalent cAd3 vaccine is undergoing testing by NIAID as well as by collaborators in the United Kingdom and the West African country of Mali. In October 2014, GSK and World Health Organization partners began an additional, larger clinical study of the monovalent vaccine in Lausanne, Switzerland. A booster vaccination designed to follow the cAd3 vaccination and induce a more durable response is being developed. The booster vaccine, a modified Vaccinia virus Ankara (MVA) including a gene from the Zaire Ebola virus, is scheduled to enter Phase I testing in 2015. In addition, NIAID and the Department of Defense (DOD) are conducting Phase I trials of another vaccine candidate, a recombinant vesicular stomatitis virus (rVSV)-vectored Ebola vaccine, in development by NewLink Genetics Corp. In partnership with GSK, DOD, the Government of Liberia, and NewLink, plans are underway to advance the cAd3 and rVSV-vectored Ebola vaccines to Phase II/III efficacy testing, including in West Africa.

In addition to vaccine candidates in Phase I trials, NIAID has supported a number of Ebola virus vaccine candidates along the product development pipeline. NIAID is supporting the biotechnology company Profectus BioSciences, Inc., to develop a multivalent rVSV-vectored vaccine candidate against Ebola and Marburg viruses. The Profectus BioSciences' monovalent Ebola vaccine has transitioned from NIAID to BARDA for advanced development. NIAID also is supporting the biopharmaceutical company Crucell in their development of a multivalent Ebola/Marburg vaccine using recombinant adenovirus vector platforms. NIAID played an instrumental role in the collaboration between Johnson & Johnson (parent company of Crucell) and Bavarian Nordic on a two-dose (prime-boost) vaccination regimen. Crucell contributed its multivalent Ebola/Marburg vaccine and Bavarian Nordic contributed its MVA-vectored vaccine for the two-dose vaccination regimen that began Phase I testing in early 2015.

NIAID intramural scientists are collaborating with academic researchers and have produced two Ebola vaccines that have been shown safe and protective in monkeys. Clinical lots of the two vaccines are currently being manufactured, and Phase I trials are planned for mid-2015. The first, an inactivated vaccine with the glycoprotein from Zaire Ebola virus expressed in a recombinant rabies vaccine construct, provides protection against rabies and Ebola virus disease in monkeys. This candidate was recently licensed to Exxell BIO of St. Paul, Minnesota, which aims to

advance the product through clinical testing and potential commercialization. The second vaccine, which is a live attenuated vaccine targeted against Zaire Ebola virus, is distinctive as it will be administered as a nasal (mucosal) immunization.

3. What initiatives are underway at the Department of Health and Human Services (HHS) to improve care for patients who are infected with Ebola today?

NIAID Response: The National Institutes of Health has developed and will implement a randomized, controlled trial to examine a variety of potential therapeutic interventions for Ebola virus disease. The first intervention to be tested is the monoclonal antibody cocktail known as ZMapp. The study will be conducted simultaneously in the United States and Liberia, with possible extension to other countries in West Africa.

4. Given many of the well-reported supply challenges with mass-producing and manufacturing Ebola drug treatments, such as ZMapp and others, in the near-term pipeline of Ebola experimental and investigational treatments, do you see potential options that could have the drug supply available to actually treat thousands of Ebola patients in West Africa?

NIAID Response: NIAID is committed to working with our partners to evaluate candidate Ebola treatments and vaccines for safety and efficacy. At this point in the outbreak, we are still working to generate the evidence to show whether potential interventions are safe and effective by moving these products expeditiously along the development pipeline into clinical trials. The data from the current and planned Phase I trials will help demonstrate whether candidate Ebola vaccines and therapeutics are safe and show signs of potential efficacy. Successful candidates will be advanced to efficacy testing in larger numbers of people in West Africa. As we proceed through clinical testing, we will continue to work with our partners in the Food and Drug Administration to advance these studies as safely and quickly as possible. We will continue our longstanding and successful collaboration with the Biomedical Advanced Research and Development Authority (BARDA) to transition candidate Ebola therapeutics and vaccines for advanced development. As mentioned in the response to question 1, BARDA is supporting manufacturing activities for ZMapp in tobacco plants to make sure that the product candidate is available in sufficient quantities for upcoming clinical trials in West Africa. BARDA's Fill/Finish Manufacturing Network is filling the ZMapp product for clinical studies. Additionally, BARDA engaged other tobacco-based biopharmaceutical companies to produce ZMapp. Lastly, BARDA partnered with Genentech and Regeneron to develop and manufacture ZMapp and new Ebola monoclonal antibodies using specialized Chinese hamster ovary (CHO) cells. These CHO cell-derived monoclonal antibodies are currently being evaluated in nonhuman primate challenge studies against Ebola and, if promising, may enter clinical trials in West Africa soon. If successful in those studies, doses of the monoclonal antibodies will be manufactured at

commercial scale at these companies and the Centers for Innovation in Advanced Development and Manufacturing (CIADMs), resulting in thousands of treatment courses later in 2015.

5. What is the role and pathway to join the global coalition of clinical trials for finding effective new experimental therapies in patients with Ebola Virus Disease in West Africa?

NIAID Response: Global coordination and cooperation will be crucial to finding safe and effective therapies to treat Ebola virus disease. The National Institutes of Health (NIH) is collaborating with industry partners, Ministries of Health in affected countries, and others to advance clinical trials of experimental therapies for Ebola virus disease such as ZMapp. Ministries of Health interested in being part of the NIH studies are encouraged to make a formal request to the U.S. Department of Health and Human Services.

6. How would a treatment that focused on surviving the deadly complications of Ebola rather than the virus itself be tested in the coalition forming for clinical trials in West Africa?

NIAID Response: Treatments focused on surviving the complications of Ebola would have the same endpoint as treatments focused on the virus, namely whether the treatment improves survival of individuals with Ebola virus disease. The National Institutes of Health has developed and will implement a randomized, controlled trial to examine a variety of potential therapeutic interventions for Ebola virus disease. The study will be conducted simultaneously in the United States and Liberia, with possible extension to other countries in West Africa.

7. For experimental treatments that are available today, what funds are being made available to rapidly test them to improve outcomes in West Africa for patients with Ebola?

NIAID Response: In the fiscal year 2015 omnibus appropriations legislation, the Congress provided \$238 million in emergency funds to NIAID to support research on Ebola vaccines, therapeutics, and diagnostics. This figure includes funds to accelerate the development of therapeutic interventions currently in the product development pipeline. Promising therapeutics will be assessed in preclinical testing including toxicology, *in vitro* testing, and animal model evaluations. Products successful in preclinical testing will be advanced to Phase I clinical trials and, if warranted, further clinical testing in West Africa. It is important to note that the emergency funding for Ebola research also will support clinical testing of Ebola vaccine candidates in West Africa. These Phase II/III clinical studies may be a crucial factor in determining how best to prevent additional cases of Ebola virus disease in the current outbreak and any future outbreaks. Finally, it is important to have additional candidates ready to be

assessed, should current candidates fail to prove safe and effective in clinical testing. The emergency funding for Ebola research will support the discovery and evaluation of additional Ebola vaccine and therapeutic candidates to ensure a robust product development pipeline.

The Honorable Dr. Michael C. Burgess

1. Please describe how the NIH is communicating with the Department of Defense on research and development of vaccines, therapeutics, and diagnostics.

NIAID Response: NIAID's longstanding and successful collaborations with the Department of Defense (DOD) are critical to accelerating efforts to develop treatments and vaccines for Ebola virus disease. NIAID is an active participant in the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), an interagency effort that coordinates federal activities on preparedness against chemical, biological, radiological, and nuclear threats, including Ebola viruses. NIAID coordinates with DOD on Ebola virus vaccines, therapeutics, and diagnostics through the PHEMCE as well as through extensive communication by NIAID and DOD scientific experts. As an active member of the PHEMCE, NIAID participates in multiple teams and committees to ensure coordination of scientific activity with PHEMCE partners, including DOD. These include Integrated Product Teams that coordinate efforts on particular threats such as filoviruses like Ebola and the Portfolio Advisory Committee that aligns Department of Health and Human Services and DOD medical countermeasure development resources.

For example, in partnership with DOD and others, NIAID is working to accelerate the development of medical countermeasures for Ebola virus. NIAID has collaborated with DOD since 2001 on the development of Ebola and Marburg vaccines based on replication-defective adenoviruses, and has conducted Phase I trials in the United States, Europe, and Africa on Ebola vaccines based on the chimpanzee recombinant adenovirus cAd3. NIAID recently expanded the collaboration with DOD to evaluate antiviral therapeutics.

Currently, NIAID and DOD are coordinating to accelerate production of two Ebola vaccine candidates. NIAID and DOD are collaborating with NewLink Genetics on an investigational recombinant vesicular stomatitis virus (VSV)-based vaccine candidate. NIAID and DOD began Phase I safety studies of this VSV vaccine candidate in the fall of 2014 at Walter Reed Army Institute of Research in Silver Spring, Maryland, and at the NIH Clinical Center in Bethesda, Maryland. Another vaccine candidate, the result of a partnership between NIAID researchers, DOD, and Thomas Jefferson University, is based on an Ebola glycoprotein expressed in a recombinant rabies vaccine construct. This rabies-based vaccine candidate provides protection against rabies and Ebola virus disease in a monkey model. In September, NIH licensed the candidate rabies/Ebola vaccine to Exxell BIO of St. Paul, Minnesota, which aims to advance the product through clinical testing and potential commercialization. Clinical lots of the vaccine are currently being manufactured, and Phase I trials are planned for mid-2015.

In addition, NIAID is partnering with DOD and the Biomedical Advanced Research and Development Authority (BARDA) on development of the Ebola therapeutic candidate ZMapp. ZMapp, developed by Mapp Biopharmaceutical, Inc., with support from NIAID and DOD, is a combination of three monoclonal antibodies that can protect monkeys from death due to Ebola virus. NIAID is working closely with partners at DOD, BARDA, and others to help determine whether ZMapp is safe and effective. BARDA is working with Mapp Biopharmaceuticals to accelerate the manufacturing of more ZMapp for further development.

These collaborations with DOD will be critical to advance the development of diagnostics, therapeutics, and vaccines for Ebola viruses. NIAID will continue to play an active role in the PHEMCE and coordinate closely with DOD and other partners to accelerate the development of effective countermeasures for the current Ebola outbreak in West Africa and any future outbreaks.