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"U.S. Government Response: Fighting Ebola and Protecting America"

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Chairwoman Mikulski, Ranking Member Shelby and Members of the Committee, thank you for inviting Regeneron to submit written testimony to help inform the Committee's work to ensure an appropriate federal investment in the ongoing effort to mitigate the current Ebola outbreak.

Regeneron Pharmaceuticals, Inc., located in Westchester County, New York, was founded in 1988 by Leonard S. Schleifer, M.D., Ph.D., who remains its CEO. Regeneron's Board of Directors includes three Nobel Laureates and five members of the National Academy of Sciences. P. Roy Vagelos, M.D., a member of the National Academy and former Chairman and CEO of Merck, is Chairman of the Board, and George Yancopoulos, M.D., Ph.D., also a member of the National Academy, is Regeneron's founding scientist and Chief Scientific Officer.

Regeneron – whose nearly 3,000 employees are dedicated to advancing science -- is the largest biopharmaceutical company in New York and the fifth largest in the world. We are a fully integrated biopharmaceutical company committed to discovering, inventing, developing, manufacturing, and commercializing important medicines for patients suffering from serious diseases. Regeneron markets medicines for eye diseases, colorectal cancer, and a rare inflammatory condition and has product candidates in development in other areas of high unmet medical need, including hypercholesterolemia, oncology, rheumatoid arthritis, allergic asthma, and atopic dermatitis. Regeneron was recognized by *Science* Magazine as the number one employer in the global biopharmaceutical industry for the third consecutive year, according to the journal's annual Top Employers Survey.

We maintain a strong foundation in basic scientific research and discovery-enabling technology, including a world-class human genetics center, and combine that foundation with our manufacturing and clinical development capabilities. Regeneron is the preeminent expert in the field of antibody-based therapies, and our expertise, together with proprietary technological assets we have developed, makes us uniquely positioned to help the U.S. Government respond to the urgent need for Ebola therapies now. **Indeed, Regeneron has already begun utilizing its staff and resources to develop an antibody-based therapy to treat Ebola and we are fully poised to produce an Ebola drug candidate that will be suitable for animal testing by the end of this year.** We are making this submission to the Committee because, in order to bring the most effective drug candidate to market on a fast track – and in order to have long-term capabilities that will deliver systematized, real-time responses to future biologic threats, it is vital that the federal government make meaningful investments in discovery, development, and manufacturing capabilities for monoclonal antibody and bispecific therapies.

SITUATION ANALYSIS

Americans and citizens around the globe will forever be at risk from emerging biological threats – natural and potentially manmade – such as viruses, bacteria, and toxins. Recent threats like the Ebola virus are highly lethal, killing up to 70% of infected individuals. In recognition of these threats, the U.S. Government has funded and established a variety of efforts to identify, develop, and in some cases stockpile countermeasures that could be deployed to protect the populace.

However, critical advances in the biotechnology industry have not yet been harnessed as a true 'Rapid Response Capability' against emerging biological threats. This testimony describes these advances in rapidly identifying and manufacturing fully human monoclonal antibodies, as well as bispecific

antibodies, and proposes several specific steps to ensuring the creation of a long-term, strategic Rapid Response Capability we are confident can be achieved.

To bring this Rapid Response Capability to fruition and make it viable for long-term U.S. public health and national security goals:

- An effective response requires use of the newest technologies available, inasmuch as doing so will dramatically speed the time in which therapies for Ebola and similar threats can be delivered with the quality and at the scale required to defeat the threat. It is imperative that the U.S. Government's arsenal against these threats expands to include critical monoclonal antibodies and bispecific antibodies that have the potential to quickly and effectively passively immunize healthcare workers and first responders for months, as well as serve as a therapy for infected persons. This treatment modality may fill the gap until a proper vaccine is developed;
- The U.S. Government should streamline its current, piecemeal approach to sourcing innovation, testing, manufacturing and commercialization capabilities to respond to Ebola and other biological threats through a singular approach; and
- The optimal structure for achieving this capability lies in a strategic public/private partnership utilizing a one-stop shop approach.

HARNESSING THE MOST ADVANCED TECHNOLOGY: MONOCOLONAL ANTIBODIES AND BISPECIFICS

An array of recent efforts targeting a treatment for viral threats, including for Ebola, have focused on developing "small molecule" (traditional, non-biologic) drugs, vaccines, and -- in a limited number of cases -- monoclonal antibodies against pathogens. Yet it is fully human monoclonal antibodies, identified using newly developed technologies, which have the potential to provide the fastest and most broadly acting rapid response for the Ebola and other biological threats.

By contrast, small molecule drugs are the most difficult to develop, with timelines of many years before candidates can be identified, and several more years before safety and efficacy can be established. For example, it took 14 years to create a truly effective multi-drug combination therapy for HIV/AIDS.

Vaccines are one of the most safe and effective ways to protect a large fraction of the population. The U.S. Government, through HHS/BARDA, has funded new technologies to create recombinant vaccines, and created pre-pandemic stockpiles against the current H5N1 strain. However, there are many pathogens for which effective vaccines have not yet been identified. Moreover, individuals with a weak immune system, like the very young and the elderly, often do not raise an adequate immune response to become protected from the pathogen. Finally, development of immunity can take from weeks to months, which is potentially too slow to protect first responders and healthcare workers in the face of an outbreak.

Fully human monoclonal antibodies (often called "mAbs") have emerged in the last decade as safe and effective drugs. One way that vaccines protect against disease is by inducing a neutralizing or sterilizing antibody response upon immunization. So in one sense, identifying and manufacturing recombinant ***fully human*** monoclonal antibodies, as well as bispecific antibodies, have the potential to provide an immediate, alternative to waiting for a vaccine response following immunization. MAbs have many characteristics that can provide advantages as a rapid response against Ebola or other biologic threats:

1. They rarely have "off-target toxicity" and therefore do not have unintended side effects.
2. Unlike vaccines, monoclonal antibodies afford immediate protection to patients.
3. Older technologies were only capable of making mouse antibodies, which could subsequently be used as mixed, or "chimeric" mouse/human antibodies (such as "ZMapp"). Since the portions of the antibody that contain mouse protein are seen as "foreign," the human immune system in many cases rejected older drugs, which ceased being effective. However, the newest technologies employed by Regeneron allow the direct identification and isolation of

fully human antibodies, which are not detected as foreign by our immune system and therefore not "rejected."

4. It is usually straightforward to identify several monoclonal antibodies directed against different parts of the pathogen, and can therefore be used in combination. As described above for HIV, many viruses can rapidly mutate to escape the inhibition by a single drug, but are well controlled by combinations of drugs that target different sequences in the virus.

RECENT INNOVATIONS CAN BYPASS DEVELOPMENT BOTTLENECKS

A series of recent innovations have revolutionized the ability to create multiple monoclonal antibodies against an emerging pathogen with unprecedented speed and simplicity. Regeneron is working at the forefront of this revolution. The combined application of these technologies allows the creation and testing of specific fully human monoclonal antibodies, which effectively protect against an emerging pathogen in animals, ***within just a few months' time***. The U.S. Government's efforts will be most effective if it uses technology that achieves the following:

1. Rapid Isolation of Specific Fully Human Monoclonal Antibodies. State of the art mouse engineering uses the natural selection processes inherent in the animal's immune system to quickly churn out literally thousands of fully human antibodies to test for superior protective qualities.
2. Create a Relevant "Genetically Humanized" Mouse Model. Efforts to create drugs against emerging pathogens are often slowed because the pathogen, a virus for example, can infect humans but not small animals such as mice. To overcome this bottleneck, mice can be "genetically humanized," in that scientists replace one or a set of mouse genes with specific human genes to enable the virus to infect the mouse. Even if the virus can infect non-human primates, it is faster, cheaper and more humane to winnow through therapeutic candidates in a mouse before final evaluation in a non-human primate and subsequent initial human trials. The most rapid methodology to make genetically humanized mice is via Regeneron's proprietary VelociGene ® technology. Regeneron has already developed many disease models with this humanization procedure.
3. Bispecific Antibodies. Create bispecific antibodies that can bind to a virus-infected cell with one arm, and recruit endogenous immune system T-cells with the other arm. Bispecific antibodies can target T-cells to effectively kill virally infected cells, and thereby prevent a viral infection from spreading to other cells in the body. Bispecific antibody technology is at the very cutting edge of biotechnology capabilities, and has the potential to dramatically improve the ability to kill infected cells. Regeneron has created a highly efficient method to create, assess, and manufacture bispecific antibodies that could uniquely meet this need, and has advanced one bispecific into oncology clinical trials to specifically kill tumor cells.
4. Creating Manufacturing Cell Lines. Monoclonal antibodies must be manufactured in cells that serve as natural antibody "factories" (known as CHO cells). While this process is standard in the biotech industry, it is a traditional bottleneck for moving a therapeutic antibody candidate into testing in animals and initial clinical evaluation. Previous processes to create a cell factory typically required 6-9 months. Regeneron's recent scientific advances have shortened this interval to **18 days.**
5. Manufacturing Clinical-Grade "GMP" Monoclonal Antibodies for Human Use. Recent advancements in biotech manufacturing focus on disposable Single Use Bioreactors (SUBs), which provide an unprecedented level of flexibility with rapid turnaround between different runs, even with different products. A Rapid Response Facility that uses SUBs could be built and scaled up rapidly. For example, a single 2,000 liter SUB could provide between 500-2,000 doses of a single antibody for human use within a few months of developing the cell line. Optimally, this Rapid Response Facility would include manufacturing capability to allow seamless use of the CHO cell factories from research to manufacture for clinical studies without the need for a lengthy multi-company transfer of manufacturing methodology. An appropriate facility could be up and running in the first half of 2016. Such a facility would be available for all future

government needs, and built to leverage the full array of latest technologies in development and manufacture. Anticipated expenses are in the range of $45 million for permitting, land, building and site preparation; of $120-140 million for building the facility; and finally $35-40 million to realize the infrastructure, including commissioning, IT, automation and qualification.

BENEFITS OF STREAMLINING TECHNOLOGIES THROUGH A SINGLE SOURCE

There are tremendous synergies in combining state-of-the-art technologies to yield a truly unified Rapid Response Capability, including isolation of fully human monoclonal antibodies, creation of genetically humanized mouse models for infectious disease, rapid derivation of cell lines, initial manufacturing of mAbs for animal testing, and rapid and efficient manufacturing of initial clinical drug lots.

In 2014, Regeneron demonstrated a fully integrated Rapid Response Capability to create, with unprecedented speed, a fully human mAb therapy for the MERS virus, which was the cause of an outbreak of lethal pneumonia in the Middle East, and which had a mortality rate of roughly 30%. From beginning to end, the entire effort -- including isolating the human antibodies from Regeneron's patented and proprietary VelocImmune® technology, creating the genetically humanized mouse as an animal model, isolating clinic-ready cell line factories, manufacturing small scale lots of multiple antibodies, and proving that the antibodies block the virus in the genetically engineered mouse model of infection -- took only 5 months. The unprecedented speed of this highly efficient and coordinated effort could not have been achieved if multiple organizations were involved in the process. Transferring materials, know-how, and manufacturing protocols inevitably leads to loss of communication and delays and most importantly wastes critical time needed to get ahead of the threat.

A PUBLIC/PRIVATE PARTNERSHIP FOR STRATEGIC, LONG-TERM BENEFIT

Utilizing its patented and proprietary mouse engineering and cell-line development technology, Regeneron believes it can identify, develop and produce mAb therapeutics to treat Ebola faster than any other biopharmaceutical company working on this challenge. Because of these technological advantages, Regeneron can produce the type of fully human antibodies described above ***by the end of the year*** and have robust quantities of drug product available for clinical testing a few months later. Progress from there will be determined by the regulatory process in place to meet exigent needs at the time and manufacturing limitations.

Regeneron is committed to this project, and our senior staff has met with Dr. Robin Robinson, Ph.D., Director of the Biomedical Advanced Research & Development Authority (BARDA), to offer our assistance. As a result, we and BARDA have already committed to an initial collaboration where we provide fully human antibodies and bispecifics to Ebola ready for animal testing both this year and early 2015, which BARDA will then advance into animal testing that would support subsequent human clinical evaluation. We and Dr. Robinson share a sense of urgency to advance the country's preparedness for the current threat and those that will inevitably arise in the future. We and he believe that this will require a fourth Center for Innovation in Advanced Development and Manufacturing (CIADM); this one focused on mAbs and bispecific antibodies.

Regeneron has demonstrated ability to rapidly and successfully advance complex biologic medicines from conception to commercial viability in record time. We are also committing many millions of dollars' worth of investment, human capital and proprietary technology to the urgent challenge not only of finding a cure for Ebola, but of doing so in a way that recognizes and supports the long-term biologic response needs of the U.S. Government. We look forward to being part of the solution.

Thank you again, Madam Chairman and Ranking Member Shelby, for allowing Regeneron to present this testimony before the Committee and for your interest in the work being done by Regeneron. We would be pleased to be a continuing resource to the Committee on this timely and critical matter.