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**Statement by**

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**Flexible Manufacturing of Pharmaceuticals for Biological Warfare Defense**

**Submitted to the**

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Mr. Chairman, Subcommittee Members, and staff: I am pleased to be here today to discuss DARPA's efforts to ensure that the United States has the manufacturing capability we need to produce the complex pharmaceutical proteins – also known as biologics – that are a key medical component of biological warfare defense (BWD). My focus today will be on the technology DARPA is developing to quickly make a population-significant quantity of biologics used in vaccines and therapeutics for BWD.

In 1996, DARPA was authorized to conduct an independent program within the DoD to develop technologies to protect our forces against biological attack. This led to a comprehensive and aggressive BWD program that has developed sensors to detect an attack, technologies to protect people in buildings, vaccines to prevent infection, therapeutics to treat those exposed, and decontamination technologies to recover the use of an area. More recently, we have turned our attention to technology to quickly produce the complex pharmaceutical proteins (i.e., biologics) we would need to counter a BW attack.

Before I talk about DARPA's specific technology development efforts, let me touch on the threats we face and our options for responding.

### **The Evolving Threat**

A wide variety of pathogens could be used against either U.S. military forces or our civilian population, including anthrax, smallpox, tularemia, ebola, botulism, enterotoxin, and ricin. But these – as serious as they are – represent only *known* threats. In this age of genetic engineering, there is also the real risk of some completely novel and previously unknown engineered pathogen rapidly appearing to threaten us. And this is to say nothing of new threats that appear naturally and spontaneously, such as Severe Acute Respiratory Syndrome (SARS), avian influenza, and multi-drug-resistant organisms.

Let me illustrate how quickly genetic engineering is advancing today. Today you can buy a toy for ages eight and above called *DNA Explorer Kit*. This toy costs around eighty dollars and has everything you need to extract DNA and purify it. In the 1980's, this required three days in a half-million-dollar university lab filled with people with graduate degrees. Now for eighty dollars, an eight-year-old can do it in two hours.

## **Responding with Flexibility**

It is true that some of the BW threats we face are known and understood. However, others are unknown or known but could be evolving.

In the face of this uncertainty, how should we respond?

A major limitation of current pharmaceutical manufacturing technology is that it is expensive, and inflexible. You can't take a facility that is producing "Drug A" and rapidly turn it around to produce "Drug B." Given the wide variety of potential threats and the inflexibility and high cost of today's pharmaceutical manufacturing facilities, it is difficult if not impossible to use today's drug manufacturing technology to provide the surge in biologics production we could need in case of a BW attack.

If we were faced with a brand new pathogen – and even if we developed a new therapy right away – it is highly unlikely that we could use today's capability to produce enough of the drug in time to protect a meaningful fraction of the population.

DARPA has been working on technology to break out of this strategic conundrum.

We began several years ago by challenging the "One Bug, One Drug" paradigm for therapeutics to be "One Drug, Many Bugs." Instead of having only one treatment for each pathogen, we pursued broad-spectrum therapeutics so that one drug could be used against many bugs. This has been evident as we have transitioned several projects to the Chemical and Biological Defense Program's Transformational Medical Technologies Initiative (TMTI).

For example, DARPA supported work on new vaccine adjuvants such as CpG, which can increase the immune response to any vaccine. CpG is now funded for advanced development by the National Institutes of Health, and by at least four major pharmaceutical companies.

We have also developed broad-spectrum approaches to countering drug-resistant strains of certain pathogens, such as anthrax that is resistant to Ciprofloxacin. This project is now in advanced development in the Chemical and Biological Defense Programs' Joint Science and Technology Office.

DARPA is extending this logic from drug design to drug production and manufacturing. In the last few years we have been pursuing the technology to change the “One Production Line, One Drug” paradigm to “One Production Line, Many Drugs.”

DARPA’s vision is to develop pharmaceutical manufacturing technology that can respond rapidly, agilely, and inexpensively to any BW attack – whether with known or unknown pathogens. Here “rapidly” means it can scale up to large volumes quickly; “agilely” means it can produce a wide variety of products equally well; and, “inexpensively” means it can do all this at lower costs than today.

An industrial base with this capability would blunt the effect of any BW attack, and greatly diminish the strategic value of launching such attacks in the first place.

### **Accelerated Manufacturing of Pharmaceuticals Program**

The current platforms for producing large protein biologics, e.g., chicken eggs and Chinese Hamster Ovarian (CHO) cells, tend to be slow, inefficient, and expensive. For example, flu vaccines are typically grown in chicken eggs, and three eggs are required for each vaccine dose. This approach is well understood, has been in use for decades, and is suited to situations where the threat is understood and reasonably predictable, and time is not critical.

But to counter any BW threat, we need to replace these complicated, low-yield processes with very high yield, inexpensive processes that can scale up rapidly for a wide range of products.

There are two interesting but quite different approaches to accelerating manufacturing of drugs.

One way is to develop a facility that can only manufacture drugs but can manufacture many different types and can be configured quickly and efficiently. In the last few years, flexible bioreactors have been developed to produce small amounts of biologics. These bioreactors use portable, low-cost, disposable plastic components connected together to build the production line needed for a given drug or vaccine. DARPA does have a small study determining the efficacy of building a facility which seeks to combine these flexible bioreactors with new technologies to produce large protein biologics at faster and cheaper than today. This study is trying to make a business case for doing so but is not completed.

Another way is adapting the biological organisms now widely used for industrial manufacturing so that they can make highly purified drugs in extremely large quantities. These organisms, like certain bacteria, now make components of food and even laundry detergent. DARPA's Accelerated Manufacturing of Pharmaceuticals (AMP) program is enabling these organisms to rapidly and inexpensively manufacture millions of doses of life-saving vaccines or therapeutic proteins in weeks, instead of the years required today using traditional technologies such as chicken eggs or mammalian cells.

The AMP approach is showing great promise.

Let me describe some of the advanced biologics platforms that DARPA's AMP is pursuing.

First, we are working with both bacteria and fungus. These are currently the best-developed technologies, with considerable industrial experience using them to produce smaller, less complicated proteins.

Bacteria have been used for a while to make smaller proteins, like the industrial enzymes used in laundry detergents. In a few cases, such as insulin production, millions of dollars have been invested to develop bacteria that produce larger proteins.

Large fermenters can use the fungus *Neurospora*, which grows in liquid with long, thread-like cells, to produce bio-enzymes for environmental cleanup, pulp degradation, ethanol production, and boosting the protein content of animal feeds.

DARPA's AMP program wants to extend these approaches and modify these relatively simple and inexpensive organisms to make much more complicated proteins than they can now, and across a wide range of biologics. Under AMP, small quantities of some large complex proteins have been produced, but they are not yet pharmaceutical-grade, i.e., they are not produced under the U.S. Food and Drug Administration's Good Manufacturing Practice (GMP) regulations. For example, bacteria have demonstrated a high yield of 30,000 doses of raw viral vaccine per liter of culture, which would result in a process six times faster than mammalian cell based production.

We can also contrast the power of this new approach with using CHO cells. CHO cells can produce up to 500 milligrams of protein per liter and tend to be very expensive. If we could use

bacteria to produce the same protein, indications are that we could produce more than 20 times more protein per liter at dramatically reduced cost.

Beyond bacteria and fungus, which are the best understood, we are also supporting research into using plants. One example is tobacco, because it is a plant that is extremely well understood since it has been studied for years due to its economic importance. The tobacco is grown under very tightly controlled, sterile, hydroponic conditions. Special bacteria are used to infect the leaves of the plant; the bacteria cause those leaves to produce the protein we want. A hydroponic tobacco growing tray, roughly 10 feet by 10 feet, would yield sufficient protein for at least one million vaccine doses – the equivalent of using three million chicken eggs as a growth medium.

In November 2007, AMP's tobacco-based technology demonstrated the capability to produce within a month over 800,000 doses of crude influenza vaccine that was highly protective in an animal model. Tobacco has also produced an avian flu vaccine that cannot be made using eggs because it kills the eggs.

DARPA's next steps are to demonstrate that vaccines produced this way are as pure and effective as those produced conventionally. The plan is to transition these techniques to the Chemical and Biological Defense Programs' Joint Science and Technology Office for additional research and development.

We are testing these efforts to make sure they have the required speed and agility. Our researchers are preparing to produce protein, but we have not told them which specific protein they will have to produce. This emphasizes our requirement that they be ready to produce a wide variety of biologics on-demand and on short notice.

In our actual Go/No-Go test, they will have only three months to produce the specified protein in the specified quantity. This keeps them all focused on being able to make a wide variety of biologics, in quantity and very quickly.

Some, and perhaps all, of these platforms will fail which is OK. There is no stigma for a Program Manager or performer to fail on a DARPA program as long as they understand why and keep trying.

I am pleased to have had the opportunity to tell you about the exciting, ongoing research in DARPA's AMP program. We are excited about this work and its potential payoff.

We believe that not only will this new technology provide new policy options for how our Nation prepares for biological warfare threats, but it will also act as a deterrent against those who might want to use BW against us since it won't have the desired impact.