Testimony
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Dual Use Research of Concern: Balancing Benefits and Risks

Statement of

Anthony S. Fauci, M.D.

Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services

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Mr. Chairman and members of the Committee:

I am pleased to have the opportunity to discuss with you recent events related to two manuscripts, as yet unpublished, reporting research results from studies focused on H5N1 avian influenza transmissibility (spread from one animal or person to another) and pathogenesis (ability to cause disease). These manuscripts have drawn global attention and led to important and intense discourse, both in the scientific community and in the media, about the need for, appropriateness of, and conditions under which "dual use research of concern", or DURC, is conducted and its results communicated to the scientific community as well as to the public. In my testimony, I will provide an overview of dual use research, as well as the chronology of these scientific manuscripts, which have garnered unprecedented attention by the U.S. Government, the international scientific and security communities, and the public. While concerns about dual use research are not new, the Administration continues to take oversight of such research very seriously and has recently strengthened procedures to mitigate any potential risks arising from DURC as scientific progress continues.

The National Institutes of Health (NIH), part of the Department of Health and Human Services (HHS), is the Nation's premier agency for the conduct and support of biomedical research. The National Institute of Allergy and Infectious Diseases (NIAID), which I direct, is the lead component of NIH for research on biodefense against terrorist attacks with pathogenic microbes or toxins and naturally occurring emerging and re-emerging infectious diseases including seasonal and pandemic influenza. In this regard, NIAID conducts and supports

basic research on microbiology and immunology; applied research, including the development of medical countermeasures for the diagnosis, treatment, and prevention of emerging infectious diseases; and clinical research to evaluate experimental drugs and vaccines. For example, NIAID leads NIH efforts to develop a "universal" influenza vaccine designed to protect people against multiple strains of seasonal and pandemic influenza without the need for an annual vaccination. Such a vaccine would potentially save millions of lives and be of great global economic benefit.

Dual use research is research that ultimately could yield new information critical to the development of technologies needed to improve public health, such as vaccines, diagnostics, and therapeutics, but also has the potential for malevolent applications if used by people with intent to do harm. In the biomedical research community, we remain mindful that much infectious diseases research may inherently have the potential for dual use.

A smaller portion of biological research has a greater potential for yielding knowledge that could be used for harm. This subset of dual use research is known as "dual use research of concern," or DURC. DURC is research that, based on current understanding, can be *reasonably anticipated* to provide knowledge, information, products, or technologies that could be *directly* misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security. Categories of research that should be closely scrutinized for DURC potential include experiments that, for a specific

group of agents and toxins: (a) enhance the harmful consequences of an agent or toxin, (b) disrupt the effectiveness of an immunization against an agent or toxin, (c) confer resistance to clinically useful prophylactic or therapeutic interventions against an agent or toxin, (d) increase the stability or transmissibility of an agent or toxin, (e) alter the host range of an agent or toxin, (f) enhance the susceptibility of a host population to an agent or toxin, and (g) generate or reconstitute an eradicated or extinct agent or toxin[1].

Because of NIAID's lead Federal role in supporting and conducting biodefense and emerging infectious diseases research, it can be expected that NIAID has funded and will fund some measure of DURC within its research portfolio. If a particular research experiment is identified as DURC, that designation does not necessarily mean that such research should be prohibited or avoided or not widely published. To the contrary, we must balance carefully the benefit of the science to public health, the biosafety and biosecurity conditions under which the research is conducted, and the potential risk that the knowledge gained from such research may fall into the hands of individuals with ill intent. Recently, a clear example of the need to weigh this balance arose with the NIAID-supported H5N1 influenza transmissibility studies conducted by Dr. Yoshihiro Kawaoka at the University of Wisconsin and Dr. Ron Fouchier at

[1] United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern. March 29, 2012: http://oba.od.nih.gov/oba/biosecurity/pdf/united_states_government_policy_for_oversight_of_durc_final_version_032812.pdf

Erasmus Medical Center in The Netherlands. I will describe for you the context within which this research was conducted.

The Threat of Influenza

Seasonal and pandemic influenza is an ongoing threat to public health worldwide and is among the leading global causes of death due to infectious diseases. According to the Centers for Disease Control and Prevention (CDC), each year, seasonal influenza causes more than 200,000 hospitalizations and up to 49,000 deaths in the United States. Throughout the world, seasonal influenza causes three million to five million cases of severe illness each year, and an estimated 250,000 to 500,000 influenza-related deaths, according to the World Health Organization (WHO). In addition to the annual threat that seasonal influenza poses, influenza viruses can undergo extensive genetic changes, sometimes resulting in the emergence of a novel influenza virus to which the human population is highly susceptible and which is readily transmissible among humans. The emergence of such pandemic influenza viruses is unpredictable; however, the consequences can be severe. The 1918-1919 global influenza pandemic was catastrophic, killing between 50 and 100 million people worldwide and causing enormous social and economic disruption.

In the last decade, the public health community has closely monitored the emergence of highly pathogenic H5N1 avian influenza. This virus circulates in birds and has, on occasion, spread to humans who, in almost all cases, have had direct contact with infected birds. Since 2003, the WHO reports that

approximately 600 confirmed cases of H5N1 influenza have occurred in humans in more than a dozen countries. Nearly 60 percent of these reported cases have resulted in death. The grave concern over the high mortality rate associated with the H5N1 virus has, to this point, been balanced by the apparent inability of the virus to transmit efficiently from human to human. However, should this virus mutate to transmit more efficiently among people, while retaining its ability to cause disease, it would create the potential for a widespread influenza pandemic.

NIAID Research on Influenza

For decades, NIAID has supported basic influenza research to investigate pathogenesis, viral evolution, host immune response to the virus, adaptation of the virus to the host, and the complex factors affecting transmissibility of influenza within and among species. Results from such basic research lay the foundation for more precise surveillance of emerging new viruses as well as the design of new diagnostics, drugs, and prevention tools, and are applicable to seasonal epidemic and pandemic strains alike. For example, basic research on the molecular structure of the influenza virus has led to advances in the development of improved influenza vaccines. Recently, NIAID researchers demonstrated that a “prime-boost” gene-based vaccination strategy could activate the immune system and lead to broadly neutralizing antibody responses against a range of influenza viruses, signaling that we are getting closer to a universal vaccine that could protect people against multiple strains of seasonal and pandemic influenza viruses.

A critical goal of influenza research is to understand how pandemic influenza viruses emerge. In this regard, it is important to conduct research to address host adaptability to viruses, transmissibility within and among species, and the effect of these processes on pathogenesis. These are among the questions investigated by Drs. Kawaoka and Fouchier and their colleagues in the highly publicized studies that we are discussing today. Elucidation of the mechanisms by which genetic mutations and other changes occur and may lead to an influenza pandemic could have important implications for influenza outbreak prediction, prevention, diagnosis, and treatment. For example, it would be important to determine if a virus that has enhanced transmissibility in animal models would remain sensitive to existing anti-influenza drugs and be inhibited by the immune responses elicited by existing vaccines. In addition, knowledge of a particular genetic mutation or set of mutations that facilitates influenza transmission in humans may be crucial for use in global surveillance of emerging pandemic influenza viruses.

H5N1 Studies and DURC

The process of genetically manipulating organisms, such as bacteria and viruses, and then identifying and analyzing the positive or negative effects of these mutations on biological functions has historically been central to infectious diseases research. Such experiments have helped to identify molecular targets on pathogenic microbes and have led to the development of currently available

products, such as vaccines for influenza, polio and chicken pox virus, as well as a newer vaccine for smallpox (MVA) and therapeutics for hepatitis C.

Using standard molecular biology and virology techniques, Drs. Kawaoka and Fouchier constructed variants of H5N1 avian influenza viruses in order to identify which genetic mutations might alter the transmissibility of the virus as well as determine their effect on pathogenicity. In their studies, these investigators employed a standard influenza animal model, the ferret. The ferret is a useful, though imperfect, model of human influenza. Though the results of scientific experiments in ferrets cannot always be directly extrapolated to humans, they are the best model available to study transmissibility and pathogenicity of influenza viruses as they might apply to humans.

Drs. Kawaoka and Fouchier submitted manuscripts to the journals *Nature* and *Science*, respectively, in which they described the increased transmissibility in ferrets of the H5N1 viruses modified in their laboratories. NIAID scientific program staff, who had been informed of the results in the manuscripts, recognized that the results of these studies might constitute DURC and referred the manuscripts to the NIH Office of Biotechnology Activities, the office that manages the National Science Advisory Board for Biosecurity (NSABB). The NSABB is an independent Federal advisory committee chartered to provide advice, guidance, and leadership regarding biosecurity oversight of dual-use research to all Federal departments and agencies with an interest in life sciences research.

Review of H5N1 Studies

In November 2011, the NSABB completed a review of the Kawaoka and Fouchier manuscripts and, in December 2011, recommended that the general conclusions summarizing the novel outcome of the studies be published due to the importance of the findings to the public health and research communities, but that the manuscripts should not include the methodological and other experimental details that could enable replication of the experiments. The NSABB also recommended a rapid and broad international discussion on dual-use research policy concerning H5N1 influenza. Lastly, the NSABB discussed the possibility of a voluntary moratorium on broad communication of such results. NIH and HHS responded quickly, accepting the recommendations and delivering them to the authors and the journals who agreed to consider the recommended redaction on the condition that the government develop a mechanism for restricted circulation of non-redacted manuscripts. The influenza research community led by the two authors in question also responded by initiating a voluntary moratorium on H5N1 influenza transmissibility studies.

On February 16 and 17, 2012, the WHO held an international non-decisional and non-binding meeting to discuss the issues related to the H5N1 influenza research. Drs. Kawaoka and Fouchier presented additional data related to the manuscripts, and Dr. Fouchier clarified data in his original manuscript.

A summary of the main points of the discussion reflects that, from a public health perspective, publishing the full manuscripts at a later date was preferable

to publishing in redacted form, and emphasizes the importance of biosafety and biosecurity measures and enhanced communication of the balance of the risks versus benefits of such research.

At the request of NIH, Drs. Kawaoka and Fouchier submitted revised manuscripts for review by the NSABB. With the further clarification of the data and methodology provided in the revised manuscripts, consideration of new non-public epidemiological information, and a security briefing on H5N1 influenza, the NSABB recommended that the revised manuscripts be published in full. The NSABB members concluded that the clarified data do not appear to provide information that would immediately enable misuse of the research in ways that would endanger public health or national security. According to the NSABB, "new evidence emerged that underscores the fact that understanding specific mutations may improve international surveillance and public health and safety."

DURC Oversight

Beyond the Kawaoka and Fouchier manuscripts, we remain deeply mindful of the potential risks of DURC. We must continually examine and balance the immediate and long-term benefit of the critical research for the public health with the risk that the conduct of certain types of DURC and/or the broad communication of the findings might enable a bioterror attack or accidental release of a microbe. NIH plays a role— which we take very seriously— in assessing whether the potential benefits of DURC outweigh the risks, and in mitigating any such risks.

The review and oversight of NIAID research is a dynamic process that occurs in multiple steps to ensure that the research we conduct and support is based on a sound scientific rationale, is relevant to our mission to conduct research in immunology and infectious diseases to improve health and alleviate suffering, and is conducted safely with minimal risk to the researchers and community. Through internal research portfolio reviews and with input from outside experts, NIAID develops research agendas that outline research priorities and highlight important research opportunities. As with all NIH research grants and contracts, research applications and proposals for individual projects are peer-reviewed by external and internal subject matter experts and advisors for scientific merit and public health relevance. Once research is initiated, NIH-supported investigators submit annual research progress reports, which are reviewed by NIH scientific program staff. Institutional Biosafety Committees, with oversight from the NIH Office of Biotechnology Activities, provide review of recombinant DNA research and pertinent biosafety measures at the institutional level where such research is conducted. For domestic research on Select Agents and toxins, the CDC and the U.S. Department of Agriculture provide biosafety and biosecurity oversight through site visits, personnel screening, security checks, and biosafety, biosecurity, and training compliance. The screening of personnel is done in partnership with the Department of Justice. For NIAID-supported research on Select Agents and toxins outside of the United States, NIAID has executed an agreement for CDC to perform similar site visits and assessments. Both the Wisconsin and Dutch laboratories have been

inspected multiple times and have been found to be in compliance with recommended biosafety and biosecurity practices. Finally, as I mentioned above, the NSABB provides advice and guidance on DURC to NIH and other Federal agencies that conduct, support, or have an interest in life sciences research, including reviewing specific DURC at the request of NIH, as was the case with the Kawaoka and Fouchier manuscripts.

Enhancing Federal Oversight of DURC

Concurrent with the recent focus on the Kawaoka and Fouchier studies, the U.S. Government has formalized a policy for the oversight of DURC. This policy, which was released for internal U.S. Government use on March 29, 2012, strengthens ongoing efforts in DURC oversight and establishes regular review of U.S. Government-funded or -conducted research on certain high-consequence pathogens and toxins for its potential to be DURC. The policy requires that Federal agencies assess the potential risks and benefits of such DURC projects and determine whether risk is generated by access to the information, products, or technologies resulting from the research. Based on this assessment, the Federal agency, in collaboration with the institution or researcher conducting the research, must develop an appropriate risk mitigation plan or take other actions if it is determined that the risk cannot be adequately mitigated.

Conclusion

The NIAID-supported research by Drs. Kawaoka and Fouchier on the transmissibility of H5N1 remains important to global health. Although concerns about the potential dual use applications of their studies brought much global attention to this research, when complete information about these studies became available and data were clarified, the NSABB determined that the benefit of communicating the results of these studies outweighed the risk of potential misuse of the information in the manuscripts.

We are committed to addressing concerns about DURC in order to maintain public confidence in the biomedical research enterprise and its critical contributions to public health and national security. The new U.S. Government policy on DURC oversight will strengthen existing processes to further ensure that we fully assess the benefits and risks of DURC, mitigate potential risks where they exist, and communicate responsibly about the importance of such research and the safety and security of its conduct.