

October 1, 2007

European Commission
Bio-preparedness Consultation
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Dear Commission Staff,

The Center for Biosecurity of the University of Pittsburgh Medical Center (UPMC) and the Center for Transatlantic Relations of the Johns Hopkins University welcome the opportunity to provide joint comment on the European Commission's Green Paper on Bio-preparedness. Our two centers are based at United States (U.S.) universities and have been collaborating with colleagues in Europe on transatlantic biosecurity and bio-preparedness issues since 2002. The initial phase of our work resulted in the widely recognized *Atlantic Storm* exercise in 2005 (www.atlantic-storm.org) which was a tabletop simulation of a transatlantic bioterrorist attack.^{1, 2}

Introductory Comments

The threat posed by destabilizing epidemics of infectious disease – bioterrorism, pandemic influenza, emerging infectious diseases, etc. – requires sustained attention and investment by the transatlantic and global communities. Bioterrorism, in particular, is an urgent and growing threat driven by the ongoing revolution in the life-sciences. These advances will lead to tremendous improvements in the entire sphere of human existence – health, agriculture, the environment, materials science, energy. However, this same knowledge can be used for malevolent purposes.

Effective bio-preparedness will require new organizational arrangements between the health and security arms of governments and also between the public and private sectors. The Commission's Green Paper on Bio-preparedness is an important signal that the European Union (EU) is actively working on bio-preparedness across all 27 Member States and the broader international community. The EU should also be recognized for the important steps it has taken in the last few years to improve regional bio-preparedness, including creation of the Health Security Committee, the ECDC, and Health Threat Unit (C3) at DG-SANCO as well as the bolstering of emergency communications via RAS-BICHAT and training via exercises (e.g. New Watchman, Common Ground).

Role of the European Bio-Network (EBN)

Efforts to build a European consensus on bio-preparedness policy and practice could be greatly assisted by the creation of a “European Bio-Network” (EBN). The EBN’s mandate, as described in the Green Paper, could be expanded beyond proposing scientific safety standards to a more comprehensive mission that includes assessments of national and regional public health preparedness activities, status of medicines and vaccines to counter infectious disease threats, and EU and global activities to improve bio-preparedness capacity and coordination. It should also address issues related to bioterrorism, not only naturally occurring disease. An expanded EBN would greatly benefit from the input of the ECDC (on preparedness and response activities) and the EMEA (on the status of medicines and vaccines). An International Advisory Board of eminent health and security experts from other nations should be considered for the EBN.

Laboratory Safety and the Select Agent List

Prevention efforts are critical, and all appropriate actions should be taken to prevent development of biological weapons, and proliferation of biothreat pathogens. However, the nature of biology makes detection and preemption of a pending bioterrorist attack unlikely. The globalization of biological knowledge and the increasing commoditization and commercialization of biological techniques mean that a small group of individuals, with a minimal “footprint,” can gather anywhere in the world and develop a biological weapon for use in a terrorist attack.³⁻⁵ This is in stark contrast to nuclear weapons. This new paradigm for biological weapons means that a significant focus for bio-preparedness should be placed on medical and public health response and recovery activities, as well as on microbial forensics for attribution of an attack.

The EU can make an important contribution to development of clear and globally practiced biosafety standards. Such standards will protect not only the lab workers but the general public and the environment. This is especially true for high-containment laboratories (BSL-3 and BSL-4 in the U.S.). The Center for Biosecurity recently held a workshop on high-containment labs and concluded that they should: 1) have robust training programs, 2) rigorously analyze accidents and “near-misses” and disseminate lessons learned, and 3) proactively engage with the public in nearby communities to achieve mutual understanding.⁶ The research done in high containment labs is critical to bio-preparedness efforts, but it must be done safely.

It would also be extremely beneficial to outbreak response if there were global, standardized procedures for quickly exchanging biological and clinical samples of infectious agents across national borders during an outbreak.⁷ While it only took eight weeks to determine the structure of a key SARS protein in the midst of the 2003 outbreak, four weeks were spent “obtaining the DNA for the viral proteins from collaborators...and getting it through customs.”⁸ The aforementioned EBN could play an important role in the development of EU biosafety and sample transport standards.

The creation of lists of dangerous pathogens that require special regulations and security measures is a step that the EU should carefully consider before taking. The U.S. has had legislation and regulations in place for many years that govern work with pathogens on the

Select Agent List (managed by the U.S. Centers for Disease Control and Prevention (CDC)).⁹ A similar list for agricultural threats is managed by the U.S. Department of Agriculture (USDA). However, the Select Agent Program, and even stricter “biosurety” rules established by the U.S. Department of Defense (DOD) for its laboratories, may actually be disadvantaging biodefense research and development in the U.S. for a number of reasons:

- The static nature of the Select Agent List does not adequately reflect the evolving nature of the biothreat – from newly emerged pathogens, or modified versions of known organisms. Judging preparedness using such a list may result in a false sense of security.
- Bacteria and viruses are replicating entities; one bacterial cell can produce trillions of progeny. Most of the pathogens of concern are available in the wild, not just in laboratories. Additionally, many viruses can now be constructed de novo in the laboratory using synthetic biology techniques, and it will not be long before bacteria can be synthesized as well.¹⁰⁻¹⁴ These factors significantly weaken the security benefit from inventorying and controlling access to lab stocks of pathogens.
- The Select Agent Program is not without significant tangible and intangible costs to research. While some scientists have increased their work on select agents since 2001, many others have moved away from these organisms fearing the regulatory burdens and associated costs of paperwork and upgraded security.⁵ Research activities at the U.S. Army Research Institute for Infectious Diseases (USAMRIID), a global leader in the study of tropical diseases and biothreat agents, has had significant increases in costs and human resource requirements to comply with new DOD “biosurety” regulations.¹⁵

In early 2007, the U.S. government announced an important strategic change to their biodefense countermeasure policy.^{16,17} Instead of focusing solely on “one-bug, one-drug” medical countermeasures (i.e. “fixed defenses”), the country would focus increasingly on the development of “flexible defenses” – medicines, vaccines, and enabling platform technologies that will have broad spectrum application to an array of biological threats stemming from both bioterrorism and natural epidemics.^{18,19} This shift is partially an acknowledgment that static lists of threat agents are problematic and stockpiles of agent-specific countermeasures for more than a handful of top threats (e.g. anthrax and smallpox) are not practicable or affordable.

As it evaluates the feasibility and utility of lists of biothreat agents, the EU may also seek to obtain a copy of the U.S. government’s 2006 Bioterrorism Risk Assessment which was prepared by the Department of Homeland Security (DHS). The assessment included 28 biological agents that could lead to deliberate exposure of civilian populations.²⁰ Genetically engineered threats, to be considered in future DHS risk assessments, will further expand the number of agents. A wide array of pathogens can cause large-scale casualties, and, apart from a few top-level threats (e.g. anthrax and smallpox), they cannot be easily ranked.

International Cooperation

The EU should work proactively on bio-preparedness with other institutions and mechanisms, including NATO, the G8 and WHO – both for surveillance and response activities. The international community must plan for coordinated responses to bioterrorist attacks and

epidemics. Such plans should include strategic and operational details commensurate with those conducted by larger international security organizations for more traditional threats. For decades EU Member States (and for most also collectively through NATO) have planned their response to all kinds of military crises. Planning with that degree of rigor and operational detail is also needed to cope with potential biological threats of international consequence; such operational planning requires cooperation between the EU and its most important security partners.

The threat of biological weapons requires a more holistic approach than just stockpiling vaccines or training more doctors. It means integrating public health and national security communities with a focus on cooperation across borders. Various potential channels come to mind. As mentioned above, one mechanism could be an International Advisory Group to the European Bio-Network. A second channel would be an EU-U.S. consultative mechanism on bio-preparedness within the U.S.-EU New Transatlantic Agenda framework, tasked to report on ways to improve U.S.-EU coordination at an upcoming U.S.-EU Summit. A third channel would be an EU-NATO consultative mechanism to address coordinated planning and emergency response, and including key health facilities such as vaccine production plants in critical infrastructure protection. While the G8 Global Partnership seeks to reduce the threat posed by weapons of mass destruction, its principal focus has been on nuclear issues; biosecurity has often been an orphan of such programs and must be accorded both higher priority and resources commensurate to the challenge. The issue for the WHO is to augment its capacity to respond to the health and medical consequences of biological attacks or pandemics. Although WHO scientists and health officials are highly capable, *Atlantic Storm* showed that even experienced politicians have unrealistic ideas of what the WHO would be able to deliver in a crisis, given its budgetary, political and organizational limits.^{1,2}

Biosecurity challenges underscore the fact that “internal” and “external” security are intrinsically linked. A number of EU governments have explicitly made this link in recent security documents, and pointed to the need for new approaches. Many EU Member States agreed to work together through NATO to address these issues through the NATO Comprehensive Approach exercise launched at the 2007 Riga Summit. The EU itself should consider elements of an “EU Comprehensive Approach” to “networked security” that draw upon synergies between traditionally domestic and foreign affairs/defense ministries within nations, as well as new cooperative mechanisms between various international institutions, such as EU, NATO, UN, and WHO. These mechanisms could be especially beneficial for EU member states whose national biosecurity resources may not be well developed. Capacities for response vary significantly across the transatlantic community.

Developing Medical Countermeasures

Efforts to bolster the EU’s capacity to develop medical countermeasures (i.e. therapeutics and vaccines) should take into account lessons from ongoing U.S. efforts. To be successful, the program must have sufficient funding (given the significant costs of developing a new medical product) and a strong partnership between government and industry.

Results for the U.S. countermeasure development programs have been mixed, frustrating both government authorities and the biopharmaceutical industry. The U.S. government and the industry have limited experience working closely together, which has caused tensions and misunderstandings.²¹ Additionally, current government funding of the program, while significant, is not sufficient given the wide array of threats and the costs of developing just a single new medical countermeasure. (The BioShield countermeasure procurement program has \$5.6 billion over 10 years,²² but it can cost over \$800 million to develop a new medicine.²³)

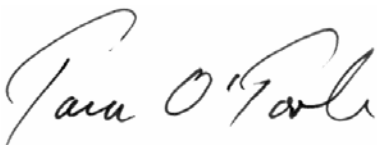
U.S. Government officials and private-sector stakeholders have been working to overcome these challenges and build more effective partnerships. In 2006 and 2007, HHS convened its annual stakeholders conference to strengthen lines of communication between government, industry and academia. The Alliance for Biosecurity, a collaboration between the Center for Biosecurity of UPMC and 13 biopharmaceutical firms, has worked since 2005 to reach out to the U.S. government and offer suggestions to improve this critically needed partnership.²⁴

As discussed above, the strategic shift in the U.S. government away from a “one-bug, one-drug” paradigm to a “flexible defense” approach^{16, 17} may also improve the situation. Not only is this new strategy more appropriate given the unpredictable nature of the bio-threat, but it will likely be more economically attractive to the biopharmaceutical industry because these “flexible,” broad-spectrum products will have markets beyond government purchases. In the long-term it may also provide the foundation for an ambitious public-private effort to develop medicines and vaccines faster, with more agility, and less expensively – both in “peacetime” and in the response to a bioterrorist attack or other public health emergency. The positive impact of this effort on health, security, and the economy would be tremendous.

Concluding Comments

We thank the Commission for the opportunity to provide comment on the Green Paper on Bio-preparedness. Preparedness for destabilizing epidemics of infectious disease will require strong collaborations between health and security communities at the national and international level and will also need a strong partnership with the private sector. We look forward to future opportunities to assist the Commission in this important work. If you have any questions or comments, or if you would like to talk further with our two centers on these issues, please contact our colleague Brad Smith at the Center for Biosecurity (bsmith@upmc-biosecurity.org).

Sincerely,



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References:

1. D. S. Hamilton, B. T. Smith, "Atlantic Storm," *EMBO Rep* **7**, 4-9 (Jan, 2006).
2. B. T. Smith *et al.*, "Navigating the storm: report and recommendations from the Atlantic Storm exercise," *Biosecur Bioterror* **3**, 256-67 (2005).
3. J. B. Petro, T. R. Plasse, J. A. McNulty, "Biotechnology: impact on biological warfare and biodefense," *Biosecur Bioterror* **1**, 161-8 (2003).
4. J. B. Petro, D. A. Relman, "Public health. Understanding threats to scientific openness," *Science* **302**, 1898 (Dec 12, 2003).
5. G. Kwik, J. Fitzgerald, T. V. Inglesby, T. O'Toole, "Biosecurity: responsible stewardship of bioscience in an age of catastrophic terrorism," *Biosecur Bioterror* **1**, 27-35 (2003).
6. G. K. Gronvall, J. Fitzgerald, A. Chamberlain, T. V. Inglesby, T. O'Toole, "High-containment biodefense research laboratories: meeting report and center recommendations," *Biosecur Bioterror* **5**, 75-85 (Mar, 2007).
7. G. K. Gronvall, R. E. Waldhorn, D. A. Henderson, "The scientific response to a pandemic," *PLoS Pathog* **2**, e9 (Feb, 2006).
8. A. Pollack, "Company Says it Mapped Part of SARS Virus," *New York Times*, July 30, 2003.
9. CDC, "Select Agent Program," <http://www.cdc.gov/od/sap/>, accessed September 18, 2007.
10. C. Lartigue *et al.*, "Genome transplantation in bacteria: changing one species to another," *Science* **317**, 632-8 (Aug 3, 2007).
11. H. O. Smith, C. A. Hutchison, 3rd, C. Pfannkoch, J. C. Venter, "Generating a synthetic genome by whole genome assembly: phiX174 bacteriophage from synthetic oligonucleotides," *Proc Natl Acad Sci U S A* **100**, 15440-5 (Dec 23, 2003).
12. J. Cello, A. V. Paul, E. Wimmer, "Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template," *Science* **297**, 1016-8 (Aug 9, 2002).
13. L. Y. Chan, S. Kosuri, D. Endy, "Refactoring bacteriophage T7," *Mol Syst Biol* **1**, 2005.0018 (2005).
14. F. A. B. G. Bio *et al.*, "Engineering life: building a fab for biology," *Sci Am* **294**, 44-51 (Jun, 2006).
15. K. Carr, E. A. Henchal, C. Wilhelmsen, B. Carr, "Implementation of biosurety systems in a Department of Defense medical research laboratory," *Biosecur Bioterror* **2**, 7-16 (2004).
16. The White House, "Homeland Security Presidential Directive 18: Medical Countermeasures against Weapons of Mass Destruction," <http://www.whitehouse.gov/news/releases/2007/02/20070207-2.html>, accessed September 19, 2007.
17. HHS, "PHEMCE Strategy and PHEMCE Implementation Plan," <http://www.hhs.gov/aspr/barda/phemce/enterprise/strategy/index.html>, accessed September 19, 2007.
18. D. A. Relman, "Bioterrorism--preparing to fight the next war," *N Engl J Med* **354**, 113-5 (Jan 12, 2006).
19. G. K. Gronvall *et al.*, "Flexible Defenses Roundtable Meeting: Promoting the Strategic Innovation of Medical Countermeasures," *Biosecur Bioterror* **5**, 271-277 (2007).
20. Committee on Methodological Improvements to the Department of Homeland Security's Biological Agent Risk Analysis, "Interim Report on Methodological Improvements to the Department of Homeland Security's Biological Agent Risk Analysis," (National Research Council, 2007).
21. G. K. Gronvall *et al.*, "Biomedical Advanced Research and Development Authority (BARDA) roundtable," *Biosecur Bioterror* **5**, 174-9 (Jun, 2007).
22. HHS, "Chemical, Biological, Radiological, and Nuclear (CBRN) Funding Activities," <http://www.hhs.gov/aspr/barda/procurement/cbrnactivities.html>, accessed September 19, 2007.
23. J. A. DiMasi, R. W. Hansen, H. G. Grabowski, "The price of innovation: new estimates of drug development costs," *J Health Econ* **22**, 151-85 (Mar, 2003).
24. Alliance for Biosecurity, "Home Page," <http://www.allianceforbiosecurity.org>, accessed September 19, 2007.