United States Department of Health & Human Services
Office of the Secretary
Office of the Assistant Secretary for Preparedness and Response (ASPR)

Screening Framework Guidance for Synthetic Double-Stranded DNA Providers

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Challenges and Concerns

- Synthetic biology and the underlying technologies together can provide significant scientific, health, and economic benefits.
- Nucleic acid synthesis technology is a potentially enabling technology for the *de novo* reconstruction of dangerous pathogens, either in part or in whole.
  - *De novo* synthesis of naturally-occurring pathogens
    - Access to sequences and organisms of concern
    - Evasion of current regulatory and physical access controls (e.g., U.S. Select Agents, Australia Group, pathogen security processes and procedures)
  - *De novo* synthesis of novel biological agents
    - Pathogens with unique properties
- Development of any oversight mechanism must…
  - balance the need to minimize the risk of misuse with the need to ensure that science and innovation are encouraged; and
  - involve engagement of the synthetic nucleic acid industry, the scientific community, and other stakeholders.

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Genesis of the Synthetic DNA and Security Interagency Process

2007

COMMENTARY

DNA synthesis and biological security

Hans Bügl, John P Danner, Robert J Molinari, John T Mulligan, Han-Oh Park, Bas Reichert, David A Roth, Ralf Wagner, Bruce Budowle, Robert M Scripp, Jenifer A L Smith, Scott J Steele, George Church & Drew E

A group of academics, industry executives and security experts propose an oversight framework to address over the security of research involving commercial DNA synthesis.

DNA synthesis allows the direct construction of genetic material starting from information and raw chemicals[1]. Improvements in synthesis technology are accelerating innovation across many areas of research, from the development of renewable energy to the production of fine chemicals, from information processing to environmental monitoring, and from agricultural productivity to breakthroughs in human health and medicine. Like any powerful technology, DNA synthesis has the potential to be purposefully misapplied. Misuse of DNA-synthesis technology could give rise to both known and unforeseeable threats to our biological safety and security. Current government oversight of the DNA-synthesis industry falls short of addressing this unfortunate reality.

Here, we outline a practical plan for developing an effective oversight framework for the DNA-synthesis industry[2]. The resulting framework serves three purposes. First, it promotes biological safety and security. Second, it encourages the further responsible development of synthetic biology technologies and their continued, overwhelmingly constructive application. And third, it is international in scope. Our plan by past and ongoing discussions security issues associated with [DNA] technology[3,4] and represents the views of all founding mem

Figure 1 Our framework calls for the immediate and systematic implementation of a tiered synthesis order screening process. To promote and establish accountability, individuals who orders for DNA synthesis would be required to identify themselves, their home organization relevant biosafety information. Next, individual companies would use validated software to synthesis orders against a set of select agents or sequences to help ensure regulatory comp flag synthesis orders for further review. Finally, DNA synthesis and synthetic biology compa work together through the ICPS, and interface with appropriate government agencies (worki to rapidly and continually improve the underlying technologies used to screen orders and id potentially dangerous sequences, as well as develop a clearly defined process to report bad fails outside of agreed-upon guidelines. ICPS, International Consortium for Polynucleotide

Hans Bügl, John P. Danner, Robert J. Molinari, John T. Mulligan, David A. Roth & Ralf Wagner are members of the International Consortium for Polynucleotide Synthesis; Hans Bügl and Ralf Wagner are at GENEART; John P. Danner, George Church & Drew Endy are at Codon Devices; Robert J. Molinari & David A. Roth are at CODA Genomics; John T. Mulligan is at Blue Heron Biotechnology; Han-Oh Park is at Bionavi; Bas Reichert is at BaseClear B.V.; Ralf Wagner is at the University of Regensburg Molecular Virology & Gene Therapy Unit, Institute of Medical Microbiology and Hygiene; Bruce Budowle, Robert M. Scripp, Jenifer A. L. Smith & Scott J. Steele are at the US FBI; George Church is in the Department of Genetics, Harvard Medical School; Drew Endy is in the Department of Biological Engineering, MIT; George Church & Drew Endy are at the multi-institution US National Science Foundation Synthetic Biology Engineering Research Center. e-mail: endy@mit.edu

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BIOTECHNOLOGY RESEARCH IN AN AGE OF TERRORISM

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

ADDRESSING BIOSECURITY CONCERNS RELATED TO THE SYNTHESIS OF SELECT AGENTS

~ DRAFT REPORT AND RECOMMENDATIONS ~

APPROVED BY THE

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

October 2006

2006

SYNTHETIC GENOMICS | *Options for Governance*

Michele S. Garfinkel, The J. Craig Venter Institute, Rockville, Maryland, Drew Endy, Massachusetts Institute of Technology, Cambridge, Massachusetts, Gerald L. Epstein, Center for Strategic and International Studies, Washington, District of Columbia and Robert M. Friedman, The J. Craig Venter Institute, Rockville, Maryland

October 2007

2007

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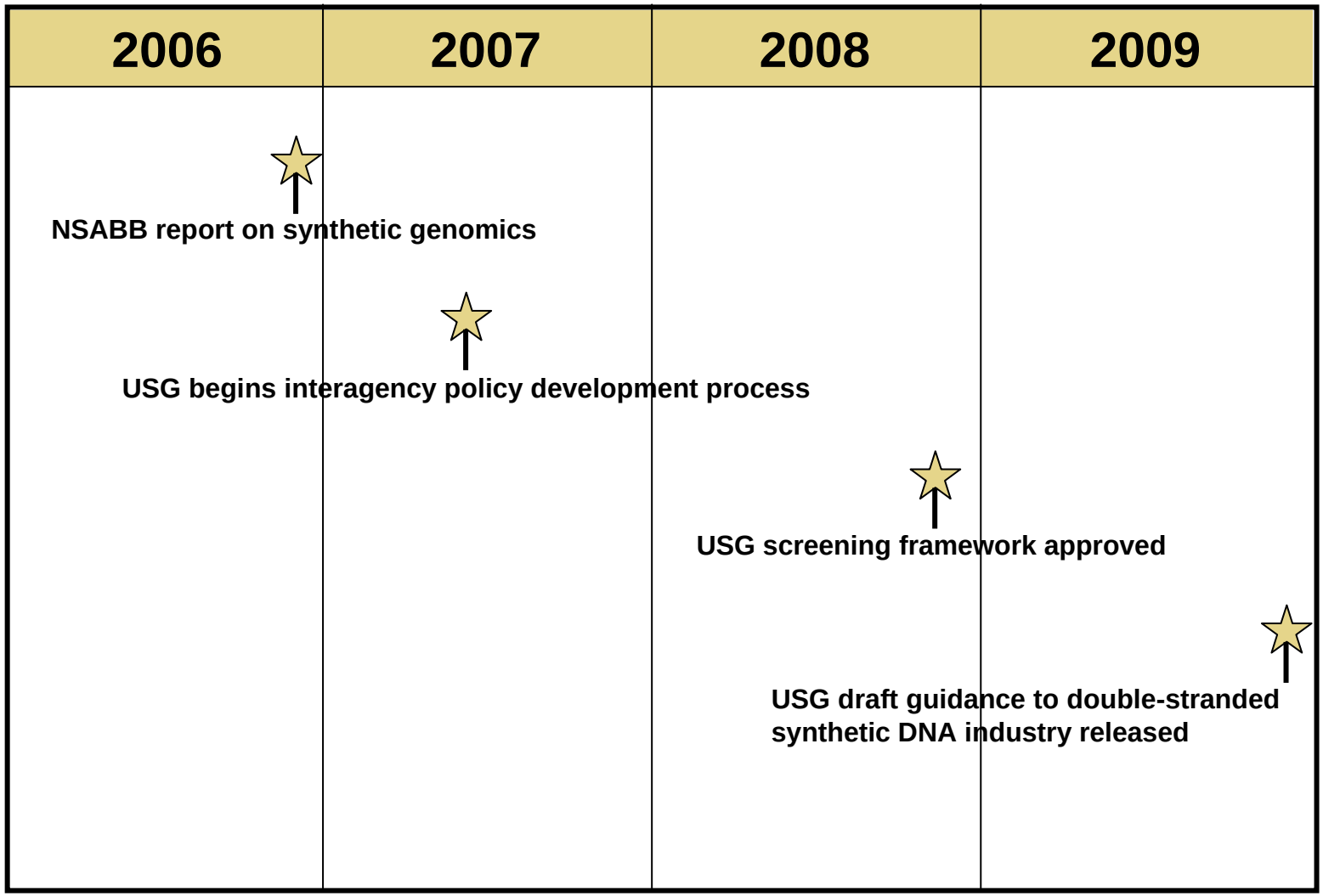
Key Milestones for USG Efforts on Synthetic DNA and Security



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USG Development of a Screening Framework

- Overarching goal:
  - Minimize the risk that unauthorized individuals or individuals with malicious intent will gain access to toxins and organisms of concern through the use of nucleic acid synthesis technologies; simultaneously minimize any negative impacts on the conduct of research and business operations
- Key elements:
  1. Appropriate sectors of the synthetic nucleic acid industry
     - dsDNA gene and genome synthesis sector
  2. Mechanism(s) by which a screening framework should be pursued
     - Voluntary- Greater efficacy and reduced negative economic impact
  3. Principles and objectives of screening
     - Providers should know customers and products they are selling
  4. Process for enabling timely response to orders of concern
     - Protocols for contacting USG
  5. Enabling development of tools to facilitate implementation
  6. Evaluating implementation and impact(s)

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Summary of Guidance Recommendations

- The U.S. Government recommends that all orders for synthetic double-stranded DNA 200 base pairs (bps) in length or greater be subject to a screening framework that incorporates both sequence screening and customer screening.
- *Customer Screening*
  - The U.S. Government recommends that, for every order, synthetic nucleic acid providers:
    - Verify the customer's identity.
    - Screen customers against several lists of proscribed entities.
    - Check for 'red flags.'
  - In any case where *customer screening* raises a concern, providers should conduct *follow-up screening.*

Summary of Recommendations, Continued

- *Sequence Screening*
  - The U.S. Government recommends that:
    - Nucleic acid sequences be screened against GenBank using a ‘‘Best Match’’ approach to identify nucleic acids that are unique to Select Agents and Toxins.
    - For foreign orders, nucleic acids be screened using a ‘‘Best Match’’ approach to identify nucleic acids that are unique to pathogens and toxins on the Commerce Control List.
    - Sequence screening be performed for both DNA strands and the resultant polypeptides derived from translations using the three alternative reading frames on each DNA strand (or six-frame translation).
    - Sequence alignment methods should permit the detection of hidden ‘‘sequences of concern’’ as small as 200 bps.
    - In any case where *sequence screening* raises a concern, providers should conduct *follow-up screening*.

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Summary of Recommendations, Continued

- *Follow-up Screening*
  - When customer screening reveals any ‘red flags’ or sequence screening identifies a sequence of concern, the U.S. Government recommends that
    - Providers ask for information regarding the customer’s proposed end-use of the order to assess their need and the scientific legitimacy of their work.
    - Providers take additional steps to verify the customer’s identity and need.
- *Domestic and Foreign Orders*
  - The U.S. Government reminds providers to check against various lists of restricted entities before filling every order; these lists vary for domestic and foreign customers.
- *Contacting the U.S. Government*
  - In cases where *follow-up screening* cannot resolve concerns raised by *customer screening* or *sequence screening, or when providers are otherwise unsure about whether to fill an order*, the U.S. Government recommends that providers contact relevant agencies.

Summary of Recommendations, Continued

- *Sequence Screening Software and Expertise*
  - The U.S. Government recommends that:
    - Providers select a sequence screening software tool that utilizes both a global and local sequence alignment technique.
    - Providers have the necessary expertise in-house to perform the sequence screenings, analyze the results, and conduct the appropriate follow-up research to evaluate the significance of dubious sequence matches.
- *Records Retention*
  - The U.S. Government recommends that providers retain electronic copies of customer orders for at least eight years.

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Next Steps

- Draft Guidance was posted for public comment in the Federal Register on November 27, 2009. It will be open for public comment for a period of 60 days until January 26, 2010.
- Please see http://edocket.access.gpo.gov/2009/E9-28328.htm for instructions on submitting comments.
- Comments can be submitted electronically to asprfrcorrespondence@hhs.gov.
- Public engagement regarding the Guidance will continue.
- At the conclusion of the public comment period, the U.S. Government will review and consider public comments for incorporation into the Guidance.
- The final Guidance will then be publicly released.
- An interagency group will be established to monitor the implementation and to evaluate the effectiveness of the Guidance.

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Thank you.