This document is scheduled to be published in the
Federal Register on 11/03/2020 and available online at
federalregister.gov/d/2020-24265, and on **govinfo.gov**

Billing Code: 4150-37

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Review and Revision of the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

AGENCY: Office of the Secretary, Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services.

ACTION: Notice.

SUMMARY: Synthetic biology is a multidisciplinary field of research that involves the design, modification, and creation of biological systems and holds broad promise to advance both basic and applied research in areas ranging from materials science to molecular medicine. However, synthetic nucleic acids and associated technologies may also pose risks if misused. To reduce the risk that individuals with ill intent may exploit the application of nucleic acid synthesis technology to obtain genetic material derived from or encoding Select Agents and Toxins and, as applicable, agents on the Export Administration Regulations' (EAR's) Commerce Control List (CCL), the U.S. Government issued guidance in 2010 providing a framework for screening synthetic double-stranded DNA (dsDNA). This document, the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* (Guidance), sets forth recommended baseline standards for the gene and genome synthesis industry and other providers of synthetic dsDNA products, regarding the screening of orders, so they are filled in compliance with U.S. regulations prohibiting the possession, use, and transfer of specific pathogens and biological toxins. The other goals of the Guidance are to encourage best practices in addressing biosecurity concerns associated with the potential misuse of these products to inflict harm or bypass existing regulatory controls and to minimize any

negative impacts on the conduct of research and business operations. Rapid and continued advances in nucleic acid synthesis technologies and synthetic biology applications necessitate periodic reevaluation of associated risks and mitigation measures. We invite public comments on whether and, if so, how the Guidance should be modified to address new and emerging challenges posed by advances in this area.

Please submit all comments related to this request for information (RFI) through the web form on the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA website at https://www.phe.gov/syndna/update2020.

DATES: Responses to this RFI must be received no later than 12 p.m. (ET) on the revised submission deadline of January 4, 2021. This notice was originally published with an earlier date. Please note that the close date for comments has been changed from the original notice.

FOR FURTHER INFORMATION CONTACT: Dr. C. Matthew Sharkey; Division of Policy; Office of Strategy, Policy, Planning, and Requirements; Office of the Assistant Secretary for Preparedness and Response; U.S. Department of Health and Human Services; phone: 202-401-1448; e-mail: Matthew.Sharkey@hhs.gov; website: https://www.phe.gov/syndna/update2020.

SUPPLEMENTARY INFORMATION:

*Disclaimer and Important Notes**:*** The U.S. Government is seeking feedback from life sciences stakeholders, including from the commercial, health care, academic, and non-profit sectors; federal and state, local, tribal, and territorial (SLTT) law enforcement organizations; SLTT governments; and others, including the members of the public. The focus of this RFI is to help inform whether updates or modifications of the Guidance are needed and, if so, what updates or modifications are desired. The U.S. Government will

review and consider all responses to this RFI. The U.S. Government will not provide reimbursement for costs incurred in responding to this RFI. Respondents are advised that the U.S. Government is under no obligation to acknowledge receipt of the information received or to provide feedback to respondents with respect to any information submitted under this RFI. Responses to this RFI do not bind the U.S. Government to any further actions related to this topic. Respondents are welcome to answer all or any subset of the questions and are strongly advised to not include any information in their responses that might be considered attributable, business sensitive, proprietary, or otherwise confidential, as comments may be made available for public review.

Categories and Questions:

Scope of the Guidance

Nucleic acid synthesis technologies are fundamental for biomedical research and allow for the generation and modification of some viruses, bacteria, and toxins. Such technologies serve as tools to advance important research to understand such agents better as well as in developing medical countermeasures. Additionally, dsDNA synthesis could pose biosecurity risks, including enabling individuals with ill intent or who are not authorized to possess Select Agents and Toxins (or, for international orders, items listed on the CCL) to obtain them using materials ordered from providers of synthetic dsDNA. The Guidance sets forth recommended baseline standards for the gene and genome synthesis industry and other providers of synthetic dsDNA, regarding the screening of orders, to ensure they are filled in compliance with Select Agent Regulations (SAR) and CCL and to encourage best practices in addressing biosecurity concerns associated with the potential misuse of their products to bypass existing regulatory controls. The U.S. Government – after receiving feedback from the scientific community and synthetic

biology industry stakeholders – developed the Guidance to align with providers' existing protocols, to be implemented without unnecessary cost, and to be globally extensible for U.S.-based providers operating abroad and for international providers. The Guidance recommends synthetic dsDNA providers perform customer screening, sequence screening, and follow-up screening to verify the legitimacy of the customer, the principal user, and the end-use of the sequence. The following questions address how the Guidance could be modified to identify nucleic acid sequences that pose biosecurity risks for follow-up screening, if deemed necessary. Please include explanations, examples, or potential benefits and drawbacks in your responses.

Should the focus of the Guidance extend beyond the Select Agents and Toxins list and CCL?

Are there potential benefits and/or downsides to screening for sequences not on the Select Agents and Toxins list or CCL?

Should the scope of the Guidance be broadened beyond synthetic dsDNA? If so, how? Should the scope of the Guidance be broadened to other synthetic nucleic acids? If so, what synthetic sequences? Or, should the scope of the Guidance be broadened beyond providers of synthetic dsDNA? If so, to whom? Why?

Should the scope of the Guidance be narrowed, either in terms of types of sequences screened or the audience of the Guidance? Why or why not?

Sequence Screening

The Guidance currently suggests follow-up screening for synthetic dsDNA orders, with the greatest percent identity (Best Match), over each 200 nucleic acid segment, and the corresponding amino acid sequence, to regulated Select Agents and Toxins and, as

applicable, the CCL. The following questions seek to understand whether the Guidance should be modified from a technical perspective.

Should the Guidance be further clarified or otherwise updated to identify embedded "sequences of concern" within larger-length orders? If so, how?

Are there approaches other than the Best Match, using the Basic Local Alignment Search Tool (BLAST) or other local sequence alignment tools, to check against the National Institutes of Health's (HIH's) GenBank database that should be considered? What are the benefits and/or downsides of those approaches compared with the current Guidance?

Are there other approaches (e.g., predictive bioinformatics tools) that could be utilized to identify sequences of concern for follow-up screening?

Are there other considerations that would be appropriate (e.g., batch size) in decisions about whether to conduct follow-up screening, such as oligonucleotide orders in quantities that indicate they are intended for use in assembling a pathogen genome directly?

Biosecurity Measures

The Guidance recommends that dsDNA orders be screened for sequences derived from or encoding Select Agents and Toxins and, for international customers, dsDNA derived from or encoding items on the CCL. The U.S. Government recognizes that there may be concerns that synthetic dsDNA sequences not unique to Select Agents and Toxins or CCL agents may also pose a biosecurity risk. The U.S. Government also recognizes that many providers have already instituted measures to address these potential concerns. The ongoing development of best practices in this area is commendable and encouraged, particularly considering continued advances in DNA sequencing and synthesis

technologies and the accelerated rate of sequence submissions to public databases such as the NIH's GenBank. However, owing to the complexity of determining if pathogenicity and other material properties pose a biosecurity risk and to the fact that many such agents are not currently encompassed by regulations in the United States, generating a comprehensive list of such agents to screen against was not feasible when the Guidance was released in 2010. The following questions pertain to how the biosecurity risks arising from the potential misuse of genetic sequences should be assessed.

Is maintenance and use of broader list-based approach(es) now feasible? If so, how might this approach be realized? If not, what are major roadblocks to implementing this approach? Since the release of the original Guidance, have providers or other entities developed customized database approaches, or approaches that evaluate the biological risk associated with non-Select Agent and Toxin sequences or, for international orders, sequences not associated with items on the CCL? If so, how effective have they been, and have there been any negative impacts?

Are there other security or screening approaches (e.g., risk assessments, virulence factor databases) that would be able to determine potential biosecurity risks arising from the use of nucleic acid synthesis technologies? What are the potential opportunities and limitations of these approaches?

Given that nucleic acid sequences not encompassed by SAR and the CCL may pose biosecurity risks, are there alternative approaches to the screening mechanism that could be established? If such approaches have been established, how effective have they been, and have there been any negative impacts?

Customer Screening

The Guidance suggests that if either customer screening or sequence screening raises any concerns, providers should perform follow-up screening of the customer. The purpose of follow-up screening is to verify the legitimacy of the customer and the principal user, to confirm that the customer and principal user placing an order are acting within their authority, and to verify the legitimacy of the end-use. If follow-up screening does not resolve concerns about the order or there is reason to believe a customer may intentionally or inadvertently violate U.S. laws, providers are encouraged to contact designated entities within the U.S. Government for further information and assistance. The following questions address how the Guidance could be modified to improve follow-up screening of customers.

What, if any, mechanisms for pre-screening customers or categories of customers for certain types of orders, if any, should be considered to make secondary screening for providers of synthetic oligonucleotides more efficient?

Are there additional types of end-user screenings or follow-up mechanisms that should be considered to mitigate the risk that synthetic genetic materials containing sequences assessed to pose biosecurity risks are transferred to a second party who does not have a legitimate purpose to receive them?

Minimizing Burden of the Guidance

The Guidance sets forth recommended baseline standards for the gene and genome synthesis industry and other providers of synthetic dsDNA products. Although voluntary, it places upon dsDNA providers the responsibility for screening sequences, customers, and end-users. In considering updates to the Guidance, the U.S. Government seeks approaches that minimize undue negative impacts of customer and sequence screening

on the synthetic biology industry and the life sciences research community. The following questions are meant to elicit insights into how these responsibilities may have impacted synthetic dsDNA providers and customers.

Does implementation of the current Guidance unduly burden providers of synthetic dsDNA? If so, how could it be modified without compromising effectiveness?

Have customers experienced delays in receiving orders of synthetic dsDNA due to screening?

Have there been any undue burdens, financial, logistical, or otherwise since implementing the Guidance? If so, has it increased, especially as other costs associated with dsDNA synthesis have decreased?

What challenges, if any, do the recommendation to retain records of customer orders, "hits," and/or follow-up screening for at least eight years present for your organization?

How might potential changes to the Guidance to expand the scope or methodologies affect the burden for providers of dsDNA and customers (including delays to scientific progress caused by extended review)?

Is your organization concerned about legal liability challenges between customers and providers?

Technologies Subject to the Guidance

The Guidance currently addresses only synthetic dsDNA and it was developed based on providers' existing protocols and technologies at that time. The life sciences field is rapidly advancing through improved bioinformatics tools, new technologies, and new discoveries. The following questions pertain to how the Guidance could be modified to address the new biosecurity risks that may be posed by advances in the life sciences.

Do other oligonucleotide types and other synthetic biological technologies, currently not covered by the Guidance, pose similar biosecurity risks as synthetic dsDNA (e.g., Ribonucleic Acid [RNA], single-stranded DNA, or other oligonucleotides)?

Are there other appropriate security measures that should be established to address the potential threats arising from the use of nucleic acid synthesis, given new and emerging technologies in the life sciences?

Are there new biosecurity risks posed by the introduction of new generations of benchtop DNA synthesizers capable of synthesizing and assembling dsDNA, RNA, single-stranded DNA, or oligonucleotides in-house that should be addressed by the Guidance?

As synthetic biology becomes an increasingly digital enterprise with large databases, digital tools, robotics, and artificial intelligence, what new risks are presented to providers and consumers of synthetic oligonucleotides?

If new risks are evident, how should these risks be addressed, keeping in mind the potential impacts on providers, customers, and scientific progress?

Additional Considerations

The U.S. Government is committed to mitigating the potential biosecurity risks associated with synthetic DNA and its applications, while minimizing undue impacts on providers, customers, and scientific progress.

Are there other mechanisms that the U.S. Government should consider for screening sequences, customers, or end-uses that may help mitigate the biosecurity risks associated with synthetic nucleotides and their applications, while minimizing undue impacts on providers, customers, and scientific progress?

(Authority: Section 301 of the Public Health Service Act, 42 U.S.C. 241; Section 605 of the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019, Pub. L. No. 116-22.)

Dated: October 28, 2020.

Robert P. Kadlec,
Assistant Secretary for Preparedness and Response.

[FR Doc. 2020-24265 Filed: 11/2/2020 8:45 am; Publication Date: 11/3/2020]