Comment on the Revised Screening Framework Guidance from the Technical Consortium for DNA Synthesis Screening

June 28, 2022

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

This comment is in response to Notice published on April 29, 2022, titled *Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides* (87 Federal Register 25495). We are writing as organizers and members of the Technical Consortium for DNA Synthesis Screening, an international and multi-stakeholder group convened by NTI | bio and the World Economic Forum to develop and disseminate a Common Mechanism for DNA synthesis screening[1] [2], which will include affordable software for DNA sequence screening along with resources to support customer screening. We plan to beta test an initial version of the Common Mechanism later this summer within the Technical Consortium and with close partners, including members of the International Gene Synthesis Consortium. Our deep technical and policy expertise in this topic area includes bioinformatics of DNA sequences, pathogen genomics, DNA synthesis industry practices, and international engagement among diverse life sciences stakeholders.

The Revised Guidance described in the *Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides* makes several positive advances beyond the original 2010 *HHS Screening Framework Guidance for Providers of Synthetic Double-stranded DNA*. We support many aspects of this Revised Guidance including:

- **Expanding the guidance to include responsibilities for third-party vendors, research institutions, principal users, and end users.** In our discussions within the Technical Consortium to develop a customer screening framework, we have found that it is difficult to depend solely on DNA providers to ensure safe and legitimate use of synthetic DNA. By assigning some responsibility to third-party vendors, institutions, and users, this Revised Guidance broadens the discussion and provides a useful basis for incorporating these additional stakeholders.

[1] World Economic Forum Insight Report, in collaboration with NTI | bio (2020) Biosecurity Innovation and Risk Reduction: A Global Framework for Accessible, Safe and Secure DNA Synthesis. January. https://www.weforum.org/reports/biosecurity-innovation-and-risk-reduction-a-global-framework-for-accessible-safe-and-secure-dna-synthesis-582d582cd4

[2] NTI (2021) NTI and WEF Convene Second Annual Meeting of DNA Synthesis Screening Technical Consortium. May 7. https://www.nti.org/newsroom/news/nti-and-wef-convene-second-annual-meeting-dna-synthesis-screening-technical-consortium/

- **Expanding the guidance to include both DNA and RNA, as well as both single- and double-stranded oligonucleotides.**

- **Expanding the guidance to include sequences as short as 50 nucleotides in length.** We believe that screening sequences at this length can reliably determine if they are a match to a potential sequence of concern or are a best match to a regulated pathogen or toxin sequence. However, lowering the threshold for screening from 200 nucleotides (from the 2010 Guidance) to 50 nucleotides will greatly increase the number of oligonucleotides that are subject to screening and will expand the number and type of providers expected to adhere to the guidance. Given that screening is already considered economically challenging for DNA providers[3], this broader recommendation should be paired with additional resources, tools, and incentives for adherence.

- **Expanding the Revised Guidance to include batch orders of oligonucleotides.** While we support this requirement in principle, it poses some practical challenges that the Revised Guidance should address. Specifically, the technical tools for screening batch orders of oligonucleotides are not fully developed, and the most effective methods are not yet clear. Rather than defining the characteristics of batch orders and the methods for screening them, the Revised Guidance should encourage the community to develop effective screening strategies and best practices. The U.S. government should support research on this topic.

- **Establishing guidance for manufacturers of benchtop DNA synthesis equipment.** We agree with the Revised Guidance recommendation that benchtop device manufacturers follow a similar framework to traditional DNA providers, which includes both customer screening and DNA sequence screening. However, the Revised Guidance should also include roles and responsibilities for institutions in the oversight of benchtop device users (including, for example, user authentication and secured access) and in ensuring that each sequence is screened so that oligonucleotides or DNA fragments representing potential biorisks are only provided to authorized users.

The Revised Guidance offers a range of recommendations that highlight the challenges related to DNA synthesis screening. The core issue is the dual challenge of encouraging DNA providers, as well as manufacturers and vendors of benchtop synthesis equipment, who currently do not screen orders and/or customers to conduct such screening, while also improving screening best practices among responsible providers—i.e., the challenge of raising the 'floor'—or baseline—level of screening while also raising the 'ceiling.' In discussions among Technical Consortium

[3] Carter SR and Friedman RM (2015) *DNA Synthesis and Biosecurity: Lessons Learned and Options for the Future.* Rockville, MD: J. Craig Venter Institute. http://www.jcvi.org/cms/research/projects/dna-synthesis-and-biosecurity-lessons-learned-and-options-for-the-future/overview/

members, we have determined that a baseline capability that can facilitate screening among current non-screeners should be: as unambiguous as possible for ease of use; defensible by including only regulated and export-controlled sequences; and reasonably transparent to garner trust.

To maximize adherence with recommended practices, the Revised Guidance should define baseline screening practices while encouraging development of best practices. Some of the recommendations listed above, such as screening batch orders of oligonucleotides, could be listed as best practices rather than baseline requirements until better screening tools are developed. There are two areas in the Revised Guidance where a delineation between baseline and best practices would be particularly helpful:

- **Expanding the guidance to include "Sequences of Concern" that are not specific to regulated pathogens or toxins.** Although we agree that biosecurity risks can arise from sequences that are not specific to regulated pathogens and toxins, the definition listed in the Revised Guidance is broad and scientifically ambiguous. This ambiguity requires expertise, time, and commitment to resolve, and the expanded definition will dramatically increase the number of sequences that are flagged for follow-up. The Revised Guidance should include this definition as a best practice rather than a baseline requirement.

- **Recommending strict security measures for databases of Sequences of Concern.** Although we recognize the potential for "information hazards" related to such databases, we believe that expanding baseline sequence screening practices to DNA providers who do not currently screen, particularly in an international context, will require that we prioritize trust and transparency where possible. After much discussion within the Technical Consortium, we have determined that a broader distribution of a biorisk database is appropriate when it is limited to established virulence factors from regulated pathogens or listed toxins that are already found in publicly available resources.[4] Such a biorisk database forms the basis of our baseline Common Mechanism. The Revised Guidance should clarify that databases with a definition of sequences of concern that is limited in this way can be more transparently shared to facilitate a baseline level of screening. We support the use of additional security measures for advanced databases with a broader definition of sequences of concern, which incorporate expert curation efforts and/or sequences of concern that are not

[4] This ambiguity arises due to limitations in our scientific understanding of virulence factors and how they function in different contexts. For example, approximately 70% of known virulence factors in pathogenic organisms are also found in non-pathogenic bacteria and do not contribute to virulence or pathogenicity in these contexts. (See: Niu, C, et al (2013) Common and pathogen-specific virulence factors are different in function and structure. *Virulence* 4(6): 473-82.)

widely publicly recognized. Such advanced databases are more likely to be used in support of screening best practices among a more limited number of DNA providers.

We applaud the U.S. government for releasing this Revised Guidance and opening an important, valuable discussion on these challenging topics. As the Technical Consortium moves forward with testing and dissemination of the Common Mechanism among DNA providers and manufacturers of benchtop DNA synthesis devices, we will continue to seek opportunities to coordinate and harmonize our approach with this new Guidance.

Sincerely,

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