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U.S. Department of Health and Human Services
200 Independence Ave. SW
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Re: Review and Revision of the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

Submitted electronically at:
https://www.phe.gov/Preparedness/legal/guidance/syndna/Pages/update2020.aspx

On behalf of the Engineering Biology Research Consortium (EBRC), I would like to express our appreciation for the opportunity to submit these comments in response to your request for information on Review and Revision of the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA. EBRC is a non-profit, public-private partnership dedicated to bringing together an inclusive community committed to advancing engineering biology to address national and global needs. We showcase cutting-edge research in engineering biology, identify pressing challenges and opportunities in research and application, and articulate compelling research roadmaps and programs to address these challenges and opportunities. One of our four focus areas is on facilitating dialogue among all stakeholder in support of advancing security in the field of synthetic biology. Our Security Working Group is comprised of synthetic biology professionals from academia, industry, and government and we hope that they can continue to serve as a resource for your work on the guidance.

As you note in the RFI, the technology used to synthesize genetic material along with the synthetic biology applications for these materials has advanced considerably in the last 10 years since the guidance was initially released. The advancements are dramatically changing many industries for the good, while also creating new challenges for implementing the screening practices outlined in the guidance. Moreover, this growth in capabilities also means that screening results themselves are increasingly complicated, requiring advanced expertise in bioinformatics for successful implementation of biosecurity screening systems and molecular biology for result interpretation. Many synthetic genetic materials providers recognize the need for enhanced screening practices and, as such, have implemented improvements over and above the 2010 guidance. However, these efforts have resulted in disparities among providers and, thus, gaps in national security. We believe that the guidance should be adapted to accommodate the growth that we have witnessed in this field and we commend you for taking this step to do so.

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

First, we would like to communicate our support for moving beyond a sequence screening approach that focuses on the Select Agents and Toxins listed by the Federal Select Agent Program (FSAP), or for international customers, items on the Commerce Control List (CCL). The current approach has become inefficient as the vast majority of sequences in an organism's genome do not 'endow or enhance' pathogenicity. Further, sequences of concern are being missed by those who are only applying the standards recommended in the 2010 guidance as there are sequence components outside of these lists

that, alone or in combination, could be used for harm. We believe a more efficient and effective approach would be to focus on individual sequences as units of control rather than species and that this requires that the Department of Health and Human Services (HHS) to provide support by defining pathogenicity-linked sequences and providing contextual information describing the role of each sequence in a well-characterized pathogenic process.

We further note that there is a lack of clarity around the definition of what constitutes a 'gene' for the purposes of export control. As part of your work to define how a synthetic genetic material provider can better identify sequences of concern, we urge HHS to ask the Department of Commerce to elaborate in updated Guidance as to what constitutes a 'gene' and to discuss the degree to which partial open reading frames or disrupted functional units can remove the requirement for an export license in some cases.

As motivating examples, the following hypothetical orders might be said to fall under the definition of a 'gene' for the purposes of export control:

- A customer orders 75% of a controlled open reading frame, preserving important functional elements in the sequence, but not the entire encoded protein.
- A customer orders a sequence that is a 'best match' to a gene from a regulated species but does not have what might be considered 'high' homology (e.g. 60% homology) to the controlled protein sequence.
- A customer orders a sequence from a gene that would be subject to a license requirement but breaks these sequences up into short (e.g. 300 base pair) segments with homologous overlapping sequences, and indicates to the synthesis provider that they intend to assemble these sequences into a longer construct.

In contrast, the following hypothetical orders may be considered to fall outside of the definition of a 'gene' for the purposes of export control:

- A customer orders 75% of an open reading frame but due to a lack of annotation, neither the customer nor the synthesis provider can determine the preservation of functional elements. If this sequence is from a controlled bacterium, it is impossible to determine whether this sequence 'endows or enhances' pathogenicity.
- A customer orders a full-length sequence but significantly changes a region that makes up a key functional domain in the protein. The customer providers literature citations to support an assertion that these changes disrupt the functional domain in a way that renders it no longer functional.

Question: 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)?

We greatly appreciate that you invite comment on the current focus of the guidance on only synthetic double-stranded DNA. Single- and double-stranded DNA conversions are commonly carried out and additionally, RNA can also be interconverted to DNA using off-the-shelf reagent kits. We also recommend that HHS extend guidance to include screening of oligonucleotide pools. Providers of synthetic genetic material regularly use oligos smaller than 200 nucleotides to assemble and manufacture gene-length DNA sequences. Given the ease of performing these tasks, we strongly urge HHS to broaden the

guidance to include all types of synthetically generated DNA and RNA, along with pools of shorter oligonucleotide sequences.

With regards to screening of oligo pools, we encourage that the guidance also explain that the 'best match' approach is not appropriate for individual, shorter DNA sequences because of the high false positive hit rate. The guidance should recommend the use of de novo sequence assembly strategies, derived from next generation sequencing analysis approaches, as one way to estimate whether a pool of oligonucleotides could be used to assemble a gene-length fragment. Only when this approach detects a potential contiguous assembly should the sequence be subject to 'best match' sequence screening.

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?

In order to minimize the likelihood that synthetic biology products and tools are used for nefarious purposes, we highly recommended that the guidance be expanded to include recommended customer screening practices for all providers (e.g. organism engineering, genetic circuit design, protein engineering firms, etc.) in the synthetic biology supply chain. This would bolster protections and convey that all product and tools providers have an equal responsibility in ensuring that these items do not end up in the wrong hands. All companies should be screening its customers against lists of denied parties and determining whether a customer has the kind of prior work that would properly frame the material they have requested. Furthermore, list of denied parties should be consolidated and shared amongst providers in an origin agnostic manner. Additionally, any company concerned that a customer may be considering using a product inappropriately should be encouraged to discuss these concerns with their local FBI WMD coordinator.

Sequence screening is a valuable tool for limiting the misuse of engineering biology and associated technologies. It should be incorporated into a holistic security strategy. Another part of that strategy should be the collection HUMINT from customer screening, newly identified sequences of concern, as well as security inputs from other sectors (e.g., names of those attempting to inappropriately acquire other potentially destructive materials); harmonizes these materials; and communicates concerns back to stakeholders in the biotechnology (and other) sectors.

Question: What, if any, mechanisms for prescreening 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?

We encourage an updated guidance document to advise against the use of so-called customer "white lists". As you are aware, this practice involves exempting customers with an extended business relationship with a synthesis provider or customers who have themselves been subject to some form of third-party biosecurity certification from screening. The lists of denied parties can change frequently and we feel that it is best practice to screen all customers each time an order is placed or shipped. In keeping with this practice, the guidance should clarify that tool and product providers ask ordering customers to provide the name of all end users. As an example, customers should provide more than just the name of the principal investigator (especially if the laboratory that the investigator is overseeing is large) or other leadership figure in an organization.

While white lists are currently impractical due largely to the open nature of much of biological research, the use of a TSA-PreCheck model may be beneficial. In this model, the level and stringency of follow up required on certain orders can be adjusted by a centralized authority and updated lists can be shared on a periodic basis. This would represent a middle ground between the full screening of every order and the carte blanche implied by white lists. We would recommend "PreChecked" individuals are screened, trained, and credentialed in a manner that is uniform and recognized by both government and industry.

Question: 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?

Yes. New generations of benchtop synthesizers are entering the market and should be included in the Guidance. How to do so is complex and, here, we give three (3) potential cases and provide *pros* and *cons* to each.

Case 1: *Benchtop synthesizers are subject to the **same expectations** for sequence and customer screening practices as a commercial entity.*

Advantages:

(1) Clairity across the industry: All products are regulated the same way regardless of the production source or method.

(2) Uniform screening ensures a consistent definition (subject to update over time) of what sequences are subject to regulatory control; this consistency does not incentivize circumvention of screening.

Disadvantages:

(1) Regulating inherently different technologies as the same can hamper innovation.

Case 2: *Benchtop synthesizers are subject to **some of the expectations** for sequence and customer screening practices as a commercial entity.*

Advantages:

(1) Rules can be tailored to differences.

Disadvantages:

(1) Inconsistent guidance can lead to confusion: benchtop devices with 'onboard' sequence screening may just be required to look for potential homology above a certain threshold to controlled organisms while centralized providers are held to a 'best match' standard. This would result in sequences failing biosecurity screening at centralized providers but being accepted on a benchtop device and vice versa (for sequences not unique to controlled pathogens, which a benchtop device checking a blacklist would never know).

(2) As benchtop device capabilities advance, the mismatch in expectations of these devices versus centralized providers may cease to be meaningful

(3) Distinctly less restrictive treatment of benchtop devices creates incentive for their use in gray-area scientific endeavors

Case 3: *Benchtop synthesizers are subject to only institutional or internal review, and not the same expectations for sequence and customer screening practices as a commercial entity.*

Advantages:

(1) Large organizations can leverage existing control systems: Many institutions have robust, existing systems that can be used as part of the risk assessment framework (e.g. IBCs)

Disadvantages:

(1) Lack of clarity across the industry: Actors who may not be able to pass sequence screening can bypass the rules to gain access.

(2) Inconsistent Institutional Review Framework: Internal culture, history, and experience can impact decision making. IBCs, for example, may yield different results at different institutions.

(3) Disincentivizes manufacturers from ensuring their devices are used responsibly. Assuming IBCs will provide oversight encourages device manufacturers to think of biosecurity as someone else's problem.

(4) Incentivizes consumers of synthetic DNA who find biosecurity screening onerous to seek out these devices explicitly to avoid screening, whether or not they intend any misuse.

Question: 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?

Yes. We highly encourage HHS to recommend that providers utilize testing that measures the performance of a company's sequence and customer screening practices. Our hope would be that this would help create uniformity in screening efficacy by helping every stakeholder to learn from implementing these complex, multilayered systems that involve layered human judgment. We feel that it is appropriate for the guidance to outline best practices in screening performance testing. Some synthetic DNA providers find 'red teaming', which involves using a third party to submit orders that should trigger follow-up screening, to be one particularly useful method. HHS should work with stakeholders to establish metrics and performance thresholds, which should at a minimum, should allow for companies to know if their screening protocols meet guidance recommendations. More importantly, the adoption of performance thresholds invites further evaluation of how to improve screening practices across the industry both within the United States and abroad.