University of Hawaii: IBC Policies & Guidelines

APPENDIX S.25 SYNTHETIC NUCLEIC ACIDS AND NUCLEIC ACID SYNTHESIS EQUIPMENT: FRAMEWORK FOR SCREENING

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Summary

The US Administration for Strategic Preparedness and Response issued screening framework guidance to provide best practices for all entities involved in the provision, use, and transfer of synthetic nucleic acids, regarding screening orders and recipients and maintaining records. The guidance encourages best practices to address biosecurity concerns associated with the potential misuse of synthetic nucleic acids. Individuals with no legitimate purpose should be prevented from accessing genetic materials that could contribute to pathogenicity or toxicity and nucleic acid synthesis equipment. Purchasing or synthesizing nucleic acids could enable individuals without a legitimate purpose to possess genetic material that would pose risks if misused.

Providers of synthetic nucleic acids, manufacturers of nucleic acid synthesis equipment, and users who order synthetic nucleic acids or purchase nucleic acid synthesis equipment are required to comply with the US Framework for Nucleic Acid Synthesis Screening. Effective October 26, 2024, US federal funding agencies will require that procurement of synthetic nucleic acids and benchtop nucleic acid synthesis equipment using federal funding be conducted through providers and manufacturers that adhere to this framework. Federally funded entities need to purchase only from those providers and manufacturers that self-attest to compliance.

Introduction

There are already established CDC and USDA APHIS regulations outlining the requirements for the possession, use, and transfer of biological select agents and toxins. In addition, the Bureau of Industry and Security (BIS) Export Administration Regulations' Commerce Control List (CCL), identifies agents and genetic sequences that require licenses before export from the United States. To further minimize risks, there is a need to assess other nucleic acid sequences that may contribute to pathogenicity or harm if introduced into new genetic frameworks (Sequences of Concern [SOCs]). Molecular biological techniques allow the conversion between different types of nucleic acids (e.g., RNA to DNA, and vice versa), so it is necessary to treat all synthetic genetic materials equally.

Definitions

Sequence of Concern (SOC): A nucleotide sequence that is a best match to a sequence of federally regulated agents (i.e., the Biological Select Agents and Toxins List, or the CCL), except when the sequence is also found in an unregulated organism or toxin. As soon as it is practical to do so, it is also recommended that sequences known to contribute to pathogenicity or toxicity, even when not derived from or encoding regulated biological agents, be treated as SOCs.

Synthetic Nucleic Acids Subject to Screening: At a minimum, DNA or RNA, single- or double-stranded, 50 nucleotides (nt) or longer should be screened for SOCs. All entities consider the potential for shorter nucleotides to be assembled into SOCs when multiple synthetic nucleic acids are ordered by the same customer in a bulk order or for multiple orders over time.

Benchtop Nucleic Acid Synthesis Equipment: Benchtop nucleic acid synthesis equipment that is intended to be used to synthesize nucleic acids for use within a research laboratory or within an institution. While this nucleic acid synthesis equipment may not be small enough to be placed on a benchtop (e.g., sits on the floor), it is still considered benchtop equipment if it is sold with the intent that it will be used by researchers individually or in a core facility in an institution.

Procedures for End Users (Customer)

1) Customers, and end users must purchase only from those providers and manufacturers that self-attest to compliance with the US. Framework.

2) Customers and end users who know that their synthetic nucleic acid order contains SOCs are encouraged to preemptively provide information that will assist the Provider or Third-Party Vendor in verifying their legitimacy.

3) Customers, and end users must only transfer synthetic nucleic acids containing SOCs to verified individuals with a legitimate use for these synthetic nucleic acids.

4) Customers and end users must maintain records of these transfers and to communicate them to their biosafety officer, or equivalent, using the responsible business practices in place in their organizations.

5) End users must record transfers of synthetic nucleic acids containing SOCs to any other individuals not listed in the original order through a Material Transfer Agreement (MTA), a contract that governs the transfer of materials between entities for use in research, or another sample tracking process. Principal Users, End Users, and institutions must retain records of SOC transfers for at least three years. Business practices already in place at institutions may be used to fulfill this recommendation.

6) Institutions and users with in-house nucleic acid synthesis capabilities, including synthesis equipment, must apply these requirements for use or transfers of synthetic nucleic acids containing SOCs.

Procedures for Providers and Vendors

1) Attest to implementing this screening framework through a statement that either is posted on a public website or provided to both the federally funded customer and federal funding agency.

2) Screen customers submitting purchase orders of synthetic nucleic acids with SOCs, and purchase orders of benchtop nucleic acid synthesis equipment, to verify legitimacy.

3) Know if the product that they are synthesizing and/or distributing contains identified SOCs.

4) Notify customers when their order contains SOCs.

5) Implement adequate security and cybersecurity measures to protect the intellectual property and identity of customers.

6) Report potentially illegitimate purchase orders of synthetic nucleic acids involving SOCs or of benchtop nucleic acid synthesis equipment. Do not fulfill the order and report an order to the FBI when follow-up screening does not resolve concerns.

7) Archive information for orders containing SOCs for at least three years: Customer information (point-of-contact name, organization, address, email, and phone number), order sequence information (nucleotide sequences ordered, vector used), and order information (date placed and shipped, shipping address, receiver name).

Procedures for Manufacturers of Nucleic Acid Synthesis Equipment <u>and Users of the Equipment</u>

1) Manufacturers must screen all customers purchasing benchtop nucleic acid synthesizers to validate customer legitimacy and only provide synthesizers to customers that have mechanisms in place to ensure that the devices are operated by legitimate users.
2) **Institutions and users** must ensure that benchtop nucleic acid synthesizers – including those that were acquired prior to this *Guidance* – are only accessed by

users with a legitimate need. If misuse or unauthorized access to benchtop nucleic acid synthesizers with the intent of obtaining SOCs is suspected, institutions must notify their FBI Field Office.

3) Manufacturers whose benchtop nucleic acid synthesizers require the use of proprietary and sole-use reagents should screen customers purchasing those reagents to verify their legitimacy, even when they were not screened when obtaining their nucleic acid synthesizer
4) Manufacturers and **customers** must implement mechanisms to track legitimate use of their equipment, including when it is potentially transferred to a new end user.
5) Manufacturers should integrate into benchtop nucleic acid synthesizers the capability to screen sequences for SOCs and to authenticate legitimate users. Manufacturers should implement this recommendation using measures that ensure cybersecurity.
6) Manufacturers should not store databases of SOCs that include sequences from unregulated pathogens or toxins on the device itself in an unencrypted manner or a manner that could allow users to extract the database.
7) Manufacturers should consider using cryptographic methods of screening that protect the contents of the order from disclosure.
8) Manufacturers are encouraged to include mechanisms to ensure the integrity of the synthesis process to prevent circumvention of the SOC screening methodology through physical or logical manipulation of the devices or reagents.
9) Manufacturers are also encouraged to include a data logging function to maintain a record of the nucleic acids synthesized on their equipment.
10) Manufacturers are encouraged to formulate a reference architecture prescribing guidance for the secure implementation, configuration, and operation of devices.

References:

1) United States Framework for Synthetic Nucleic Acid Synthesis Screening, *see* https://www.whitehouse.gov/wp-content/uploads/2024/04/Nucleic-Acid_Synthesis_Screening_Framework.pdf
2) United States Department of Health and Human Services Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids, *see* https://aspr.hhs.gov/legal/synna/Documents/SynNA-Guidance-2023.pdf