Description: In accordance with Section 1104(b) of Title XI of the Financial Institutions Reform, Recovery, and Enforcement Act of 1989, as amended, notice is hereby given that the Appraisal Subcommittee (ASC) will meet in closed session:

Location: FDIC Building, 1776 F Street, NW., Room 4085, Washington, DC 20429.

Date: October 13, 2010.

Time: Immediately following the ASC open session beginning at 10:30 a.m.

Status: Closed.

Matters to be Considered: September 22, 2010 minutes—Closed Session. Preliminary discussion of State Compliance Reviews.

Dated: October 6, 2010.

James R. Park,

Executive Director.

[FR Doc. 2010–25661 Filed 10–12–10; 8:45 am]

BILLING CODE P

FEDERAL RESERVE SYSTEM

Change in Bank Control Notices; Acquisitions of Shares of a Bank or Bank Holding Company

The notificants listed below have applied under the Change in Bank Control Act (12 U.S.C. 1817(j)) and § 225.41 of the Board's Regulation Y (12 CFR 225.41) to acquire shares of a bank or bank holding company. The factors that are considered in acting on the notices are set forth in paragraph 7 of the Act (12 U.S.C. 1817(j)(7)).

The notices are available for immediate inspection at the Federal Reserve Bank indicated. The notices also will be available for inspection at the offices of the Board of Governors. Interested persons may express their views in writing to the Reserve Bank indicated for that notice or to the offices of the Board of Governors. Comments must be received not later than October 28, 2010.

A. Federal Reserve Bank of Richmond (A. Linwood Gill III, Vice President), 701 East Byrd Street, Richmond, Virginia 23261–4528:

1. William Lee Hale and the William Lee Hale Trust, both of Bland, Virginia, acting in concert to retain control of 20.86% of the voting shares of First Regions Bancshares, Inc., Richlands, Virginia and thereby indirectly acquire voting shares of First Sentinel Bank, Richlands, Virginia.

Board of Governors of the Federal Reserve System, October 7, 2010.

Robert deV. Frierson,

Deputy Secretary of the Board.

[FR Doc. 2010–25679 Filed 10–12–10; 8:45 am]

BILLING CODE 6210–01–P

FEDERAL RETIREMENT THRIFT INVESTMENT BOARD

Sunshine Act; Notice of Meeting

TIME AND DATE: 9 a.m. (Eastern Time) October 18, 2010.

PLACE: 4th Floor Conference Room, 1250 H Street, NW., Washington, DC 20005.

STATUS: Parts will be open to the public and parts will be closed to the public.

MATTERS TO BE CONSIDERED:

Parts Open to the Public

1. Approval of the minutes of the September 20, 2010 Board Member Meeting.
2. Thrift Savings Plan Activity Report by the Executive Director.
   a. Monthly Participant Activity Report
   b. Monthly Investment Performance Review
   c. Legislative Report
3. Mid-Year Financial Audit Report.
4. Quarterly Vendor Financial Report.
5. Annual Budget Discussion.

Parts Closed to the Public

6. Confidential Vendor Information.

CONTACT PERSON FOR MORE INFORMATION: Thomas J. Trabucco, Director, Office of External Affairs, (202) 942–1640.

Dated: October 8, 2010.

Thomas K. Emswiler,

Secretary, Federal Retirement Thrift Investment Board.

[FR Doc. 2010–25854 Filed 10–8–10; 11:15 am]

BILLING CODE 6760–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

AGENCY: Department of Health and Human Services, Office of the Secretary.

ACTION: Notice.

Authority: Public Health Service Act, 42 U.S.C. 241, Section 301; HSPD–10.

SUMMARY: 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 or Toxins and, as applicable, agents on the Export Administration Regulations' (EAR's) Commerce Control List (CCL), the U.S. Government has developed Guidance that provides a framework for screening synthetic double-stranded DNA (dsDNA). This document, the *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* (the 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 that they are filled in compliance with current U.S. regulations and to encourage best practices in addressing biosecurity concerns associated with the potential misuse of their products to bypass existing regulatory controls. Following this Guidance is voluntary, though many specific recommendations serve to remind providers of their obligations under existing regulations. The framework includes customer screening and sequence screening, follow-up screening as necessary, and consultation with U.S. Government contacts, as needed.

A draft version of the Guidance was published as a **Federal Register** Notice (**Federal Register**, Vol. 74, No. 227, November 27, 2009, *Screening Framework Guidance for Synthetic Double-Stranded DNA Providers*) for public consideration and comment for a period of 60 days. Comments were reviewed and the Guidance was amended through a deliberative interagency process. The *Response to Public Comments* document, which precedes the final Guidance in the Supplementary Information section of this Notice, provides a general review of the decisions made to alter the Guidance in response to public comments. The Department of Health and Human Services (HHS) is issuing this document as the lead agency in a broad interagency process to draft the Guidance. The Guidance will be reviewed on a regular basis and revised, as necessary. For further details about the Guidance, to access public comments, and to provide ongoing feedback please refer to *http://www.phe.gov/preparedness/legal/guidance/syndna.*

DATES: The Guidance is effective on October 13, 2010.

FOR FURTHER INFORMATION CONTACT: Jessica Tucker, PhD, Office of Policy and Planning, Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health

and Human Services, 330 C Street, SW., Room 3021K, Washington, DC 20201; phone: 202–260–0632; fax: 202–205–8674; Web site: *http://www.phe.gov/preparedness/legal/guidance/syndna.*

SUPPLEMENTARY INFORMATION:

Response to Public Comments on Draft Screening Framework Guidance for Synthetic Double-Stranded DNA Providers

I. Summary

The draft Guidance document was posted as a **Federal Register** Notice on November 27, 2009, for a period of 60 days for public comment. Twenty-two individual responses were received during this time period. The American Association for the Advancement of Science hosted a meeting to solicit the views of scientists, the public, and stakeholder communities on January 11, 2010 during the public comment period; the summary report from this meeting was submitted as a formal comment. Public comments are available at the following Web site: *http://www.phe.gov/preparedness/legal/guidance/syndna.*

An interagency working group of Federal Government representatives was established to review and consider the public comments that were received; these comments informed the changes made in the final version of the Guidance. In general, public comments were received in the areas of customer screening, customer concerns, follow-up screening, and sequence screening, though some comments fell outside these categories. This *Response to Public Comments* document provides a general review of the decisions made to alter the Guidance in response to public comments in these thematic areas.

A. Customer Screening and Customer Concerns

The draft Guidance includes recommendations for providers to screen against a number of different lists of proscribed entities; the lists to screen against differ depending on whether the order is placed by a domestic or international customer. Regarding these recommendations, several comments indicated a desire for a list that combines these proscribed entities (or alternatively, for a list of "approved" customers). No changes were made in response to these comments. The indicated lists exist under several different legal authorities and are maintained by different government bodies. In order to ensure that providers are referencing the most up-to-date versions of these lists, the U.S. Government continues to recommend that providers consult the primary sources.[a] A list of "approved" customers is not practicable as it would have to be updated very frequently, given the emergence of new legitimate customers on a regular basis, and it would require that companies share their customer lists. Customers and providers should be aware, however, that there are some software packages available that may address these requests for a centralized database of consolidated lists.

Several comments were received regarding the list of "red flags" outlined in Section V.A.2 of the Guidance. Some respondents requested more guidance regarding how to respond to "red flags" raised in the customer screening process. To address these concerns, the Guidance now clarifies that follow-up screening is recommended whenever any 'red flag' raises cause for concern. Additionally, several respondents requested the deletion of the following 'red flag' which appeared in the draft Guidance: "An unusually large order of DNA sequences, including larger than normal quantities, the same order placed several times, or several orders of the same sequence made in a short timeframe." Some customers and providers have indicated that such orders are a regular part of doing business and do not pose cause for concern. The U.S. Government agrees with these assessments. Accordingly, this 'red flag' has been deleted from the final Guidance text.

Several comments also indicated that "customers" are not always equivalent to "end users," and these respondents indicated that the Guidance should be clearer in advising providers to request information about the "end user." In response to these comments, the final Guidance has been amended to define "customers" and "principal users"; most initial customer screening is focused on customers, while follow-up screening addresses both customers and principal users. "Principal users" was chosen rather than "end users," to prevent confusion with the Department of Commerce definition of "end user" vis-à-vis export control.

A few comments reflected an interest in altering the Guidance to include a process for customers to contest denied orders. No changes were made in response to these comments. Because providers of synthetic double-stranded DNA (dsDNA) already have the right to deny an order for multiple reasons, including issues unrelated to biosecurity concerns, a process to contest denied orders is not offered in this Guidance. Finally, a couple of comments indicated that customers should be notified when their orders raised any cause for concern. In follow-up screening, it is recommended that customers be contacted for additional information about their order when there is cause for concern, so customers will be made aware if their order raises a 'red flag' for the provider. Therefore, no changes were made in response to these comments.

B. Follow-Up Screening

A few comments requested additional clarity or recommendations regarding vetting orders that are placed by an individual within a larger organization or entity. As a result, the follow-up screening section has now been amended to include examples of steps that might be taken to address orders from customers that are organizations or principal users that are affiliated with a larger organization. Additionally, because a couple of comments indicated that unaffiliated customers or principal users may not have a publication record, an additional option was provided for vetting unaffiliated customers/principal users wherein the customer/principal user may provide references that can verify their identity and the legitimacy of the order.

C. Sequence Screening

The topic that elicited the most public comments was sequence screening. The issues raised can generally be separated into the following themes: type/length of DNA to screen, sequences of concern, and sequence screening methodology.

1. Type/Length of DNA to Screen

In the draft Guidance, the U.S. Government recommended that orders of synthetic dsDNA 200 base pairs (bps) and longer should be subject to a screening framework. A number of public comments critiqued this recommendation, while a few comments supported this recommendation as reasonable. Some comments stated that 200 bps is too small to be practical for providers to implement, and recommended screening sequences 1 kilobase pair (kbp) and longer. A larger number of comments stated that a 200 bp limit is not scientifically justified, and argued that because most providers already screen all synthetic dsDNA orders, the 200 bp limit should be eliminated. Finally, a small number of comments recommended that oligonucleotides, in addition to dsDNA, should be included in a screening

[a] The Department of Commerce maintains consolidated links to many of these lists on the following Web site: *http://www.bis.doc.gov/complianceandenforcement/liststocheck.htm.* Additionally, the "EAR Marketplace" also includes consolidated links to lists: *https://bxa.ntis.gov/prohib.html.*

framework. The U.S. Government agrees that a 200 bp limit is not scientifically justified and that most providers already screen all dsDNA orders. Therefore, the recommendation to eliminate the 200 bp limit was adopted, and the final Guidance now recommends that all dsDNA orders should be screened. Because crafting "agents of concern" using dsDNA via *de novo* synthesis is still easier than by using single-stranded oligonucleotides, dsDNA is the focus of this screening framework. Additionally, it is likely that implementing a screening framework would pose a significant burden for providers of oligonucleotides. Nonetheless, given the rapid developments in DNA synthesis, the U.S. Government will continue to examine this issue and may make amendments accordingly.

2. "Sequences of Concern"

A number of comments noted that many sequences that are not unique to Select Agents and Toxins may pose a biosecurity risk, but that only those sequences unique to Select Agents and Toxins (and, for international orders, those sequences unique to items on the Commerce Control List (CCL)) are characterized as "sequences of concern" within the draft Guidance. Additionally, several comments noted that non-Select Agent homologs that are closely related to a Select Agent virulence factor or pathogenicity gene could potentially be ordered and then substituted for the Select Agent sequence. These comments variously recommended that the Guidance adopt a broader definition of "sequences of concern," establish a curated database of virulence genes and "other dangerous sequences," and/or adopt a "Top Homology" screening approach (*see* discussion of Screening Methodology below).

The U.S. Government recognizes that there are concerns that synthetic dsDNA sequences not unique to Select Agents or Toxins or CCL items may also pose a biosecurity concern. However, a robust screening framework that can be consistently implemented from provider to provider requires a clear set of criteria for identifying non-Select Agent or Toxin (or non-CCL) "sequences of concern." Due to the complexity of determining whether a specific sequence corresponds to a virulence factor or pathogenicity gene or otherwise poses a biosecurity risk, and because current knowledge of virulence and pathogenicity is limited, it is not currently possible to develop clear criteria that providers could use to robustly, comprehensively, and consistently identify non-Select Agent and Toxin or non-CCL "sequences of concern" based on virulence, pathogencity, or "other danger."

In addition, many pathogens and toxins not listed on the Select Agents and Toxins lists and the CCL could nearly as easily be obtained through other means. The Select Agents and Toxins lists and the CCL are well-defined lists of high consequence pathogens and toxins that have the potential to pose a severe threat to human, animal, or plant health. Finally, the agents on the Select Agents and Toxins lists and the CCL are most relevant for these purposes because a primary goal is to prevent access to agents otherwise subject to existing regulations.

Consequently, in the final Guidance, the U.S. Government continues to define "sequences of concern" as those sequences unique to Select Agents and Toxins (and those sequences unique to items on the CCL for international orders).

The sequence screening recommendations contained in this Guidance do not preclude the use of curated databases or the development of robust criteria that can consistently identify non-Select Agent and Toxin or non-CCL sequences that may pose a biosecurity risk. The U.S. Government encourages the continued development of such databases and criteria as additional screening tools that will improve with time as additional data becomes available. To advance knowledge in this arena, the National Academies is conducting a study that will identify the scientific advances necessary to predict biological function from nucleic acid sequences for oversight of Select Agents.

3. Screening Methodology

Many of the comments on screening methodology echoed issues raised in defining "sequences of concern." A number of comments criticized the "Best Match" approach to screening, arguing that it is easily circumvented and less robust than some current industry screening practices, and proposed either screening against a centralized, curated database of "sequences of concern" or adopting a "Top Homology" approach. The curated database approach is potentially very efficient, but requires the creation of databases identifying specific features such as known pathogenic sequences, virulence factors, house-keeping genes, etc. While the acquisition of such knowledge is progressing, at this time it is not possible to provide a robust database that would identify all or even most such sequences.

In the "Top Homology" approach, human screeners examine all sequences that exceed a certain threshold of homology to a dsDNA order to determine whether or not the matching sequences are derived from Select Agents and Toxins or from genes variously described in public comments as "genes that can be intentionally abused," "risk-associated" genes, or genes that "code for virulence or other threat characteristics." This approach shares some similarities with "Best Match," though the "Top Homology" approach considers all sequences that exceed a certain threshold and "Best Match" considers the top "hit." As with the customized database approach, a "Top Homology" approach could not be meaningfully implemented without a clear set of effective criteria for determining in a consistent and non-arbitrary manner when an order should trigger further customer review. However, the clear and effective criteria needed to make such an approach work are difficult to determine. The "Best Match" approach flags only the top "hit," which meets the stated goal of identifying sequences *unique* to Select Agents and Toxins (and, for international orders, sequences *unique* to items on the CCL).

As a result, the U.S. Government continues to recommend the use of the "Best Match" approach for screening. As stated above, the U.S. Government recognizes that there are concerns that synthetic dsDNA sequences not unique to Select Agents or Toxins or CCL items may also pose a biosecurity concern. The U.S. Government also recognizes that many providers have already instituted measures to address these concerns. The Guidance sets forth recommended baseline standards for providers regarding the screening of orders so they are filled in compliance with current U.S. regulations and to encourage best practices in addressing biosecurity concerns. As such, the ongoing development of best practices in this area is commendable and encouraged, particularly in light of the continued advances in DNA sequencing and synthesis technologies and the accelerated rate of sequence submissions to public databases such as GenBank.

Minor wording changes have been made to clarify or alter the technical details of the screening methodology, including language to address the high sequence similarity of some Select Agents and Toxins with some attenuated strains of Select Agents and Toxins that have been excluded from regulation. The U.S. Government recognizes that continued research and

development may lead to new and improved screening methodologies. As new methods are developed, U.S. guidance may change accordingly. In addition, the sequence screening methodology recommendations contained in this Guidance do not preclude the use of other screening approaches that providers assess to be equivalent or superior to the "Best Match" approach.

It is significant to note that sequence screening is simply a trigger for further customer screening and decision-making and does not by itself provide a basis for determining that filling an order is likely to pose a threat.

Beyond "Best Match" comments, some public comments requested that additional software screening recommendations be provided; for example, software packages, additional screening parameters, etc. It is not the policy of the U.S. Government to recommend specific, proprietary software packages. As a result, additional screening parameters are not provided as these details are specific to individual screening packages. Finally, the recommendation to "separately" screen international orders against both the Select Agents and Toxins lists and the CCL that appeared in the draft Guidance was altered to indicate that, for international orders, screening should cover the CCL in addition to the Select Agents and Toxins lists. Whether these screens are conducted separately or simultaneously is up to the provider.

D. Other Issues

In the draft Guidance, the screening framework indicated that customer screening should precede sequence screening. Several comments noted that the order of screening is irrelevant, as long as both customer and sequence screening occur for every order. The U.S. Government agrees with these comments, and has altered the final Guidance to remove the recommendation that screening occur in a particular order.

Finally, the recommendations in the draft Guidance were directed to "commercial" providers. Some comments indicated that the U.S. Government should recommend that all providers of synthetic dsDNA follow the recommended screening framework. The U.S. Government agrees with these comments. In order to effectively meet biosecurity goals, this recommendation was adopted, and the final Guidance is directed to all providers of synthetic dsDNA. Accordingly, when the final Guidance refers to "orders" of synthetic dsDNA, this term does not necessarily imply a commercial transaction.

The Guidance will be reviewed on a regular basis and revised, as necessary. The U.S. Government recognizes that as the technology, the industry, and the nature of the biosecurity risk change, the Guidance will have to be altered, accordingly.

Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

I. Summary

Synthetic biology, the developing interdisciplinary field that focuses on both the design and fabrication of novel biological components and systems as well as the re-design and fabrication of existing biological systems, is poised to become the next significant transforming technology for the life sciences and beyond. Synthetic biology is not constrained by the requirement of using existing genetic material and thus has great potential to be used to generate organisms, both currently existing and novel, including pathogens that could threaten public health, agriculture, plants, animals, the environment, or materiel. In the United States, many such pathogens, as well as certain toxins, are defined by specific existing regulations: Namely, the Select Agent Regulations (SAR) and, for international orders, the Export Administration Regulations (EAR). 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 or Toxins and, as applicable, agents on EAR's Commerce Control List (CCL), the U.S. Government has developed Guidance that provides a framework for screening synthetic double-stranded DNA (dsDNA). This 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 that they are filled in compliance with current U.S. regulations and to encourage best practices in addressing biosecurity concerns associated with the potential misuse of their products to bypass existing regulatory controls.

Following this Guidance is voluntary, though many specific recommendations serve to remind providers of their obligations under existing regulations. Briefly, upon receiving an order for synthetic dsDNA, the U.S. Government recommends that providers perform *customer screening* and *sequence screening.* If either *customer screening* or *sequence screening* raises any concerns, providers should perform *follow-up screening.* 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 should contact designated entities within the U.S. Government for further information and assistance. This Guidance also provides recommendations regarding proper records retention protocols and screening software.

II. Introduction

Synthetic biology, unlike traditional recombinant DNA technology, is not constrained by the requirement for existing genetic material. This novel feature, along with rapid advances in DNA synthesis technology and the open availability of pathogen genome sequence data, has raised concerns in the scientific community, the dsDNA synthesis industry, the U.S. Government, and the general public that individuals with ill intent could exploit this technology for harmful purposes.

Within the U.S., microbial organisms and toxins that have been determined to have the potential to pose a severe threat to public health and safety, animal health, plant health, or animal or plant products are regulated through the SAR, administered by the Department of Health and Human Services/Centers for Disease Control and Prevention (HHS/CDC) and the U.S. Department of Agriculture/Animal and Plant Health Inspection Service (USDA/APHIS). The SAR sets forth requirements for the possession, use, and transfer of listed agents. Additionally, the EAR identifies agents and genomic sequences that require export licenses from the United States. The directed synthesis of polynucleotides could enable individuals not authorized to possess Select Agents (or, for international orders, those items listed on the CCL) to obtain them through transactions with providers of synthetic dsDNA. Such synthesis obviates the need for access to the naturally occurring agents or naturally occurring genetic material from these agents, thereby greatly expanding the potential availability of these agents.

The National Science Advisory Board for Biosecurity (NSABB) was charged with identifying the potential biosecurity concerns raised by the ability to synthesize Select Agents and providing advice on whether current U.S. Government policies and regulations adequately cover the *de novo* synthesis of Select Agents. Their report entitled *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents* was formally transmitted to the U.S. Government in March 2007.

Federal Departments and Agencies with roles in life sciences research and/or security deliberated over the NSABB recommendations and identified a series of relevant policy actions targeted to promote risk management, while seeking to minimize negative impacts upon scientific progress or industrial development.

One of the formal policy actions charged Federal Departments and Agencies to identify, evaluate, and support the establishment of a screening infrastructure for use by providers and users of synthetic nucleic acids while engaging stakeholders in industry and academia. This document provides guidance to all providers of synthetic dsDNA regarding a screening framework for synthetically-derived dsDNA orders. Specific recommendations are **in bold type** throughout the text.

In the context of this Guidance, the following definitions are applicable:

"Provider" refers to the entity that synthesizes and distributes dsDNA. A provider is understood to be an entity synthesizing dsDNA for and distributing dsDNA to a customer, not a research scientist collaborating with a colleague.[1] "Customer" refers to the individual or organization that orders or requests synthetic dsDNA from a provider, and "Principal user" is the individual that receives and ultimately uses the ordered or requested dsDNA.

III. Goals of Guidance

The primary goal of the Guidance is to minimize the risk that unauthorized individuals or individuals with malicious intent will obtain "toxins and agents of concern" through the use of nucleic acid synthesis technologies, and to simultaneously minimize any negative impacts on the conduct of research and business operations. The Guidance was developed, in light of providers' existing protocols, to be implemented without unnecessary cost and to be globally extensible, both for U.S.-based providers operating abroad and for international providers.

Providers of synthetic dsDNA have two overriding responsibilities in this context:

- Providers should know to whom they are distributing a product.
- Providers should know if the product that they are synthesizing and distributing contains, in part or in whole, a "sequence of concern".

The Guidance outlines a screening framework that will assist providers in meeting both of these responsibilities. Though certain guidance provided in this document is necessarily framed by U.S. policy and regulations, the Guidance was composed so that fundamental goals, provider responsibilities, and the screening framework could be considered for application by the international community. In particular, though the Select Agents and Toxins and the CCL-listed items that are the primary focus of the Guidance may not be relevant for all countries, the sequence screening framework can be applied to other categories of agents and toxins that may be relevant for other regions.[2]

IV. Overview: Synthetic dsDNA Screening Framework

Providers should establish a comprehensive and integrated screening framework that includes both *customer screening* and *sequence screening,* as well as *follow-up screening* when *customer* and/or *sequence screening* raises a concern.

- *Customer Screening*—The purpose of *customer screening* is to establish the legitimacy of customers ordering synthetic dsDNA sequences. Providers should develop *customer screening* mechanisms to verify the legitimacy of a customer if the customer is an organization or confirm customer identity if the customer is an individual, to identify potential 'red flags,' and to conform to U.S. trade restrictions and export control regulations.
- *Sequence Screening*—The purpose of *sequence screening* is to identify when "sequences of concern" are ordered. Identification of a "sequence of concern" does not necessarily imply that the order itself is of concern. Rather, when a "sequence of concern" is ordered, further follow-up procedures should be used to determine if filling the order would raise concern. *Sequence screening* is recommended for all dsDNA orders.
- *Follow-up Screening*—The purpose of *follow-up screening* is to verify the legitimacy of customers both at the level of the customer and the principal user, to confirm that customers and principal users placing an order are acting within their authority, and to verify the legitimacy of the end-use.

Many customers will likely volunteer information about their identity or the sequence they are ordering. Providers should corroborate this information as part of their screening framework.

The following overall screening methodology is recommended:

1. Upon receiving an order for synthetic dsDNA, the U.S. Government recommends that providers conduct both *customer screening* and *sequence screening.* In *customer screening,* providers should review the information provided by the customer to verify their corporate or individual identity (as applicable), and to identify potential "red flags." Providers should also check customers against lists of denied or blocked persons and entities maintained by the Departments of Commerce, State, and Treasury.

In *sequence screening,* the U.S. Government recommends screening the ordered sequence to identify sequences derived from or encoding Select Agents and Toxins [3] and, for international customers, providers should also screen the ordered sequence to identify sequences derived from or encoding items on the CCL.[4] Scenarios of concern may include:

a. If an ordered dsDNA product can be classified as a Select Agent or Toxin based on the SAR [3 5] or is identified as a "sequence of concern" (defined in Section V.B.1.), additional customer verification steps should be performed and may in some cases be required.

b. If an ordered dsDNA product can be classified as a Select Agent or Toxin based on the SAR, [3 5] providers must be registered under the SAR to possess the dsDNA product. Transfer of the material from the provider must be done in accordance with APHIS and CDC procedures using the APHIS/CDC Form 2 to obtain authorization for and to document the transfer. Additional information on the transfer of Select Agents and Toxins is available at *http://www.selectagents.gov.*

c. Additional restrictions or licensing requirements may apply for

[1] Transfers of synthetic dsDNA should be evaluated for conformance with the SAR and EAR even when dealing with collaborating laboratories.

[2] The CCL items that are on the Australia Group Common Control Lists are relevant for all Australia Group members (*see http://www.australiagroup.net/en/index.html*).

[3] Please see *http://www.selectagents.gov* to access the most recent Select Agents and Toxins lists.

[4] Visit *http://www.access.gpo.gov/bis/ear/ear_data.html* to access the most recent Commerce Control List and review the Export Administration Regulations. The pathogens on the Commerce Control List are derived from the Select Agents and Toxins lists and the Australia Group's three pathogen control lists. As a member of the Australia Group, the United States has made a commitment to control exports of pathogens and their genetic elements on these lists.

[5] The CDC/APHIS national Select Agent registry Web site (*http://www.selectagents.gov*) contains a guidance document entitled "Applicability of the Select Agent Regulations to Issues of Synthetic Genomics" to assist providers in identifying synthetically derived Select Agent materials that would fall under the current regulations. The regulation of Select Agents and Toxins currently includes (1) nucleic acids that can produce infectious forms of any Select Agent viruses and (2) Recombinant nucleic acids that encode for the functional form(s) of any of the regulated toxins if the nucleic acids: (i) Can be expressed in vivo or in vitro, or (ii) Are in a vector or recombinant host genome and can be expressed in vivo or in vitro.

international orders if they include an item that is listed on the CCL.[6]

2. If *sequence screening* or *customer screening* raises any concerns, providers should pursue *follow-up screening* to verify the legitimacy of the customer, the principal user and the end-use of the ordered sequence. The goal of *follow-up screening* is to assist the provider in determining whether to fill the order. If the provider encounters a scenario where they would benefit from additional assistance in assessing an order, the provider is encouraged to seek advice from the relevant U.S. Government Departments and Agencies by contacting the nearest FBI Field Office Weapons of Mass Destruction (WMD) Coordinator. The WMD Coordinator can be reached by contacting the local FBI Field Office and asking to be connected to the FBI WMD Coordinator.

V. Details: Synthetic dsDNA Screening Framework

This section provides details of the steps involved in the recommended screening framework. These steps include *customer screening, sequence screening,* and *follow-up screening.*

A. Customer Screening

Customer screening encompasses two overarching responsibilities of providers: customer verification and identification of any "red flags."

1. Customer Verification

(a) **The U.S. Government recommends that, for every order, providers of synthetic dsDNA gather the following information to verify a customer's identity:**

- **Customer's full name and contact information**
- **Billing address and shipping address (if not the same)**
- **Customer's institutional or corporate affiliation (if applicable)**

(b) To ensure compliance with U.S. regulations concerning exports and sanctioned individuals and countries, **the U.S. Government recommends that, for every order, providers of synthetic dsDNA screen customers against several lists of proscribed entities (described in Section VI).**

Lack of affiliation with an institution or firm does not automatically indicate that a customer's order should be denied. **In such cases, the U.S. Government recommends conducting *follow-up screening*.**

Additionally, the U.S. Government recognizes that many providers have instituted measures and procedures to properly vet customers. The ongoing development of best practices in customer screening is commendable and encouraged, particularly as methodologies and resources become available to further assist with customer screening.

The U.S. Government recommends that companies retain records of customer orders for at least eight years based on the statute of limitations set forth by U.S. Code of Federal Crimes and Procedures, Title 18 Section 3286.[7]

The U.S. Government recommends archiving the following information: customer information (point-of-contact name, organization, address, and phone number), order sequence information (nucleotide sequences ordered, vector used), and order information (date placed and shipped, shipping address, and receiver name).

2. "Red Flags"

In reviewing the customer's order information, providers should take into account any circumstances in the proposed transaction that may indicate that the order may be intended for an inappropriate end-use, customer, or destination. These are known as "red flags."

The following is an illustrative list of indicators that can help in identifying suspicious orders of synthetic dsDNA:

- A customer whose identity is not clear, who appears evasive about their identity or affiliations, or whose information cannot be confirmed or verified (*e.g.,* addresses do not match, not a legitimate company, no Web site, cannot be located in trade directories, etc.).
- A customer who would not be expected in the course of their normal business to place such an order (*e.g.,* no connection to life science research, biotechnology or requirement for DNA synthesis services).
- A customer that requests unusual labeling or shipping procedures (*e.g.,* requests to misidentify the goods on the packaging, requests to deliver to a private address, or requests to change the customer's name after the order is placed, but before it is shipped).
- A customer proposing an unusual method of payment (*e.g.,* arranging payment in cash, personal credit card or through a non-bank third party) or offering to pay unusually favorable payment terms, such as a willingness to pay a higher than expected price.
- A customer that requests unusual confidentiality conditions regarding the order, particularly with respect to the final destination or the destruction of transaction records.

If a review of customer information reveals one or more "red flags," the U.S. Government recommends that providers conduct *follow-up screening*. If providers are unsure about whether to fill an order, they should contact the U.S. Government for further information (described in Section VII).

B. Sequence Screening

Sequence screening, which identifies whether a requested sequence is a "sequence of concern," is intended to serve as a trigger for further *follow-up screening* and does not by itself provide a basis for determining whether an order poses a risk. Providers should screen all orders of dsDNA.

1. Identifying "Sequences of Concern"

The U.S. Government recommends that dsDNA orders be screened for sequences derived from or encoding Select Agents and Toxins and, for foreign orders, for dsDNA derived from or encoding CCL-listed agents, toxins, or genetic elements. The U.S. Government chose the pathogens and toxins identified by HHS and USDA as "Select Agents and Toxins" as an appropriate list of "agents of concern" against which providers should screen orders since:

- The list is comprised of high consequence pathogens and toxins that have the potential to pose a severe threat to human, animal, or plant health or to animal or plant products
- Their possession, use, and transfer are managed through Federal regulations.

The Select Agents and Toxins lists are reviewed biennially and updated as needed to address biosecurity concerns.[8]

The U.S. Government reminds providers to screen for items on the CCL for international orders to ensure they are in compliance with the EAR. As a member of the Australia Group, the United States requires exporters through

[6] See Category 1, ECCN 1C353 of the CCL available at *http://www.bis.doc.gov.*

[7] The eight-year statute of limitations in Section 3286 applies to the offense defined by Title 18 Section 175(b) (possession of biological agents with no reasonable justification).

[8] A list of biological agents and toxins that affect humans has been promulgated by HHS/CDC (HHS Select Agents and Toxins, 42 CFR 73.3). A list of biological agents that affect animals and animal products has been promulgated by USDA/APHIS/Veterinary Services (USDA Select Agents and Toxins, 9 CFR 121.3). A list of agents that affect plants and plant products has been promulgated by USDA/APHIS/Plant Protection and Quarantine (USDA Select Agents and Toxins, 7 CFR 331.3). Additionally, HHS and USDA promulgated a list of "overlap" agents that affect both humans and animals (42 CFR 73.4 and 9 CFR 121.4).

the EAR to obtain export licenses for exports of reading-frame length nucleic acid sequences from pathogens listed under Export Control Classification Numbers (ECCNs) 1C351, 1C352, 1C353, and 1C354.[9] The EAR also requires exporters to obtain licenses for exports of reading-frame length nucleic acid sequences from pathogens on the Select Agent list not listed elsewhere on the CCL (ECCN 1C360). The EAR requirements specifically apply to genetic elements that encode toxins or sub-units of controlled toxins or genetic elements associated with pathogenicity of controlled microorganisms.

Therefore, for the purposes of this Guidance, Select Agents and Toxins are classified as "agents of concern," and "sequences of concern" are dsDNA sequences derived from or encoding Select Agents and Toxins. For international orders, "agents of concern" also include items on the EAR's CCL, and "sequences of concern" include those dsDNA sequences derived from or encoding those items. The U.S. Government may revisit these definitions in the future in light of experience with implementation of the Guidance and scientific and technological developments.

Because the CCL and the Select Agents and Toxins lists are not identical, it is recommended that providers ensure that international orders are screened to identify sequences derived from or encoding items on the Select Agents and Toxins lists and the CCL.

If a customer orders a synthetic dsDNA product that meets the definition of a Select Agent or Toxin,[3] [5] domestic providers and customers must be in compliance with the CDC and APHIS Select Agent Regulations (42 CFR part 73, 7 CFR part 331, and 9 CFR part 121) in order to fill the order. A provider of such regulated dsDNA must be registered with CDC or APHIS in order to synthesize these materials. In addition, the provider must obtain an approved transfer form from CDC or APHIS and, for interstate transfers, a permit from APHIS (when applicable) in order to ship such products. International providers are advised that the receiving party must obtain an import permit from CDC and/or APHIS and an approved transfer form in order to receive such products. All providers are advised that receivers must hold a permit in order to receive through importation or interstate transport *any* product that meets the definition of "plant pest" (as defined at 7 CFR part 330), or any organism or its derivative which may introduce or disseminate any contagious or infectious disease of animals (9 CFR part 122).

The U.S. Government recognizes that there are concerns that synthetic dsDNA sequences not unique to Select Agents or Toxins or CCL items may also pose a biosecurity concern. The U.S. Government also recognizes that many providers have already instituted measures to address these concerns. The ongoing development of best practices in this area is commendable and encouraged, particularly in light of the continued advances in DNA sequencing and synthesis technologies and the accelerated rate of sequence submissions to public databases such as the National Institutes of Health's GenBank. However, due to the complexity of determining pathogenicity and because research in this area is ongoing and many such agents are not currently encompassed by regulations in the U.S., generating a comprehensive list of such agents to screen against is not currently feasible and hence is not provided in this Guidance.

2. Technical Goals and Recommendations for *Sequence Screening*

The U.S. Government developed the following list of specific technical goals and recommendations for a sequence screening methodology to ensure the reliable and accurate detection of synthetic dsDNA sequences derived from or encoding "sequences or agents of concern:"

The U.S. Government recommends that the sequence screening method be able to identify sequences *unique* to Select Agents and Toxins; to meet their obligations under existing regulations, for international orders, screening should also be able to identify sequences *unique* to CCL-listed agents, toxins, and genetic elements. Many DNA sequences encode genes that are required to maintain normal cellular physiology, otherwise known as "house-keeping genes." These "house-keeping genes" are highly conserved between pathogenic and non-pathogenic species. Screening methodologies that recognize highly conserved sequences such as "house-keeping genes" as positive "hits" for "sequences of concern" offer little biosecurity benefit and may impede the screening efforts. Such methodologies would produce a larger number of "hits" adding extra burden for screeners and potentially resulting in actual "sequences of concern" being overlooked. Additionally, such a system may hamper scientific research by falsely assigning sequences from closely related microbes as "sequences of concern."

The U.S. Government recommends that *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). Each amino acid is encoded by a codon, a three nucleotide sequence of DNA. The correspondence from codon to amino acid is not unique. A given amino acid may be encoded by one to six distinct codons, which means that an amino acid polypeptide can be encoded by many different DNA sequences. Consequently, to determine whether a nucleotide sequence is derived from or encodes a "sequence or agent of concern," it is necessary to screen the six-frame translation polypeptides encoded by the DNA sequences in addition to the DNA sequences themselves.

The U.S. Government recommends that sequence alignment methods should enable the detection of any "sequences of concern" in a dsDNA order. The screening routine should be capable of local sequence alignments. A sequence screening system that assesses only the overall sequence length without any local checks may not detect a "sequence of concern" embedded within a larger, benign sequence. **In order to ensure that "sequences of concern" embedded within larger sequences are not overlooked, when screening orders longer than 200 base pairs (bps), providers should use screening techniques able to detect "sequences of concern" as short as 200 bps in length.** One method that providers may consider using involves comparing overlapping 200 bp nucleotide segments (nucleotides 1–200, 2–201, etc.) and corresponding 66 amino acid sequences, over the length of the dsDNA order, to a public sequence database such as GenBank using a sequence alignment tool.

3. Sequence Screening Methodology

The U.S. Government recommends a "Best Match" approach for *sequence screening* to determine whether a query sequence is derived from or encodes a Select Agent or Toxin or, for international orders, a sequence from a CCL-listed item. In this approach, the query sequence is aligned with a database of known sequences (such as GenBank) to identify the sequence with the greatest percent identity (the "Best

[9] Definitions of terms pertinent to exports can be found in Part 772 of the EAR. Part 734 (15 CFR chapter VII, subchapter C) describes the scope of the EAR and explains certain key terms and principles used in the EAR. The EAR provisions are subject to change, as they are regularly updated pursuant to multilateral agreements.

Match") over each 200 bp nucleic acid segment and corresponding amino acid sequence (or over the entire query sequence for those dsDNA orders shorter than 200 bps). Advantages of the "Best Match" approach include: It is automatically adaptable as new sequences are added to GenBank, it is adaptable to entirely synthetic genes, it can be accomplished using publicly available databases and tools, and it does not require provider discretion in setting similarity cut-off criteria.

In this approach, a query sequence is deemed to be a "hit," and the order should be investigated further by the provider in *follow-up screening,* if the nucleotide sequence, over any span of 200 or more nucleotides (or fewer than 200 nucleotides if the query sequence is shorter than 200 bps), or if any of the six derivable 66 amino acid open reading frame (ORF) translations, is more closely related to the sequence of a Select Agent or Toxin (or CCL item, when applicable) than to any other sequence in GenBank. Due to the high sequence similarity of some Select Agents and Toxins with some attenuated strains of Select Agents and Toxins that have been excluded from regulation,[10] sequences that are "Best Matches" to these excluded strains should still be considered a "hit" and the order should be subject to *follow-up screening.*

The "Best Match" approach is intended to minimize the number of sequence hits due to genes that are shared among both Select Agents or Toxins and non-Select Agents or Toxins (or for genes shared among CCL and non-CCL items, when applicable). Nonetheless, some harmless sequences in Select Agents or Toxins (or CCL items) or those that are routinely used in scientific research may result in a "hit" during this sequence screen. **The U.S. Government recommends that providers develop, maintain, and document protocols to determine if a sequence "hit" qualifies as a true "sequence of concern;" protocols that are no longer current should be maintained for at least eight years. Additionally, providers should keep screening records of all "hits" for at least eight years, even if the order was deemed acceptable.** In cases where the provider is unable to make the determination, advice can be sought from the relevant U.S. Government Departments and Agencies by contacting the nearest FBI Field Office Weapons of Mass Destruction Coordinator.

As noted in Section V.B.1 above, the U.S. Government recognizes that there are concerns that synthetic dsDNA sequences not unique to Select Agents or Toxins or CCL items may also pose a biosecurity concern. The U.S. Government also recognizes that many providers have already instituted measures to address these concerns. The ongoing development of best practices in this area is commendable and encouraged, particularly in light of the continued advances in DNA sequencing and synthesis technologies and the accelerated rate of sequence submissions to public databases such as GenBank.

To this end, providers may also choose to use other screening approaches that they assess to be equivalent or superior to the "Best Match" approach or that supplement it, including 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. These sequence screening recommendations do not preclude the use of curated databases of non-Select Agent or Toxin or non-CCL sequences for sequence screening. The U.S. Government encourages the development of such databases as an additional screening tool that will improve with time as additional data become available. Whatever sequence screening approach a provider adopts, the approach should meet the technical requirements outlined in Section V.B.2; additionally, the provider may choose to develop additional criteria to address non-Select Agent and Toxin or non-CCL sequences. If the provider determines that an ordered product poses a biosecurity risk, the provider should conduct *follow-up screening* accordingly. **The U.S. Government recommends that providers develop, maintain, and document their sequence screening protocols within company records; protocols that are no longer current should be maintained for at least eight years.**

The U.S. Government recognizes that continued research and development may lead to new and improved screening methodologies. As new methods are developed, U.S. Guidance may change accordingly.

C. Follow-Up Screening

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.

***Follow-up screening* should be conducted if *customer screening* or *sequence screening* raises any concerns.** In any case where there are abnormal circumstances surrounding the order or the customer has ordered a "sequence of concern," **the U.S. Government recommends that providers ask for information about the customer and principal user, including the proposed end-use of the order, to help assess the legitimacy of their order.**[11] Sample end-uses of ordered synthetic dsDNA could include, but are not limited to:

- Identification of pathogenicity genes via marker-deletion mutagenesis.
- Training for threat agent detection.
- Production of organism for experimental research studies.

If not conducted previously, providers should gather the following information to verify a principal user's identity:

- **Principal user's full name and contact information.**
- **Billing address and shipping address (if not the same).**
- **Principal user's institutional or corporate affiliation (if applicable)**

If the customer or principal user is affiliated with an institution or firm, providers should contact the relevant biological safety officer, supervisor, lab director, director of research, or other relevant institutional representative in order to confirm the order, verify the customer's and principal user's identity, and verify the legitimacy of the order. If the customer or principal user is not affiliated with an institution or firm, providers should also conduct a literature review of the customer's or principal user's past research to verify his or her identity and the legitimacy of the order. If a literature review results in no publications, providers should request the unaffiliated customer or principal user provide references that can verify their identity and the legitimacy of the order. Additionally, the U.S. Government recommends that providers screen principal users against several lists of proscribed entities (described in Section VI), if this

[10] Information about attenuated strains that are not subject to the requirements of 42 CFR part 73, 9 CFR part 121, and 7 CFR part 331 can be accessed at *http://www.selectagents.gov/Exclusions.html.*

[11] As statutory precedent for requesting information about proposed end-use, providers and customers should be aware of U.S. Code Title 18 Section 175(b), which states in part that "Whosoever knowingly possesses any biological agent, toxin, or delivery system of a type or in a quantity that, under the circumstances, is not reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose, shall be fined under this title, imprisoned not more than 10 years, or both."

step wasn't already performed as part of *customer screening*.

Providers may consider other steps that could be implemented as part of *follow-up screening.* For example, when the customer is an institution or firm, providers may consider the following steps: Check the customer's contact information against standard industry and institutional directories and listings; where the customer is known by reputation, check that the contact information matches its Web page; and/or confirm customer identity though government contacts. When the customer or principal user is affiliated with an institution or firm, providers may consider the following steps: Check whether the institution's or firm's usual paperwork has been used to place the order; check that shipments will be delivered to the institution's or firm's usual address; check that the customer's and principal user's supervisors have been copied on the order or can confirm the order; check that the order has been certified by the institution or firm; and/or check that the end-use has been reviewed and approved by the institutional biosafety committee or another relevant institutional committee.

It is important to note that a provider's decision to pursue *follow-up screening* does not necessarily imply that the U.S. Government will be contacted. However, 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 as described in Section VII. **Providers should retain records of any *follow-up screening*, even if the order was ultimately filled, for at least eight years.**

VI. Recommended Processes for Domestic and International Orders

This section outlines recommendations for specific screening processes for orders from domestic and international customers. The *customer screening, sequence screening,* and *follow-up screening* protocols that are referenced in this section are defined and described in Section V. Most of the information provided in this section serves as a reminder to providers to ensure they are meeting their legal obligations not to conduct unapproved business transactions with certain proscribed entities.

A. Domestic Orders

Once a domestic customer order is received, the provider should conduct both *customer screening* and *sequence screening,* in no particular order.

1. Customer Screening

In addition to verifying the customer identity and identifying any "red flags," providers should be aware of regulatory and statutory prohibitions for U.S. persons from dealing with certain foreign persons, entities and companies. **In order to avoid violating U.S. law, providers are encouraged to check the customer against several lists of proscribed entities before filling each order, including the:**

- Department of Treasury Office of Foreign Assets Control (OFAC) list of Specially Designated Nationals and Blocked Persons (SDN List).
- Department of State list of persons engaged in proliferation activities.
- Department of Commerce Denied Persons List (DPL).

According to U.S. regulations, no U.S. persons or entities may conduct business transactions with individuals or entities on the SDN List without a license from OFAC. This list is maintained by OFAC. OFAC only provides a license to deal with individuals on the SDN List in extremely limited circumstances.[12]

According to U.S. regulations, no U.S. persons or entities may conduct business transactions with individuals sanctioned by the Department of State for engaging in proliferation activities.[13]

Additionally, the U.S. Government recommends that providers screen customers against the DPL for domestic orders. This list includes those firms and individuals whose export privileges have been denied. While the Department of Commerce only regulates exports and therefore does not require that companies screen their domestic customers against the list, it recommends that they do so, to avoid unwittingly passing on sensitive technology or materials to U.S. residents known to be involved in proliferation activities.[4]

Because the updated lists are available online, **providers should ensure they are using the most recently updated lists when screening customers or principal users against these lists.**

If there are concerns after consulting these lists, providers should seek assistance from the U.S. Government as outlined in Section VII.

2. Sequence Screening

Providers should also conduct *sequence screening.* If a "sequence of concern" is identified, providers should conduct *follow-up screening.*

B. International Orders

Once an order from an international customer is received, the provider should conduct *customer screening* and *sequence screening,* in no particular order. Providers are reminded that genetic elements of the Select Agents and Toxins, microorganisms and toxins (proteins) are controlled for export. Exporters should make sure they are in compliance with the EAR when exporting genetic elements from CCL-listed items.[4]

1. Customer Screening

In addition to verifying the customer identity, identifying any "red flags,' and complying with the rules described for domestic orders, **all providers who export products from the United States to international customers must comply with the U.S. export laws, including the International Emergency Economic Powers Act,[14] the Trading with the Enemy Act,[15] and any implementing U.S. Government regulations or Presidential Executive orders. Certain transactions with sanctioned countries may be permitted but may require a license from OFAC and/or the Department of Commerce's Bureau of Industry and Security (BIS). Currently, most transactions involving Cuba, Iran, and Sudan are prohibited. In order to comply with the U.S. export laws and regulations, providers must first determine whether a given transaction with a sanctioned country is permitted, and, if not permitted without a license or approval, obtain any appropriate export licenses or other U.S. Government permissions prior to exporting any product to sanctioned countries.**

According to U.S. regulations, no U.S. persons or entities may conduct transactions with individuals or entities on the SDN List without a license from OFAC. This list is maintained by OFAC. OFAC only provides a license to deal with individuals on the SDN List in extremely limited circumstances.[12]

According to U.S. regulations, no U.S. persons or entities may conduct business transactions with individuals sanctioned by the Department of State

[12] Additional information, including the SDN List, is available at: *http://www.treas.gov/offices/enforcement/ofac/sdn/.*

[13] Announcements of such sanctions determinations are printed in the **Federal Register** and are maintained on the Department of State's Web site (*http://www.state.gov/t/isn/c15231.htm*).

[14] Visit *http://www.treas.gov/offices/enforcement/ofac/legal/statutes/ieepa.pdf* for additional information.

[15] Visit *http://www.treas.gov/offices/enforcement/ofac/legal/statutes/twea.pdf* for additional information.

for engaging in proliferation activities.[13]

Some products may not have a specific number on the CCL and so will be designated as EAR99 for export purposes. Items designated as EAR99 do not require a license unless they are exported to countries on the embargoed list, to banned individuals, or for prohibited end-uses. **As a result, before filling an international order for any dsDNA product that cannot be classified under an Export Control Classification Number (ECCN), providers must consult several lists of such individuals and organizations according to the EAR.**[4] If the customer appears on any of these lists, additional action is required and an export license may be necessary, depending on the list.[16] These lists include the DPL, the Entity List (EL),[17] and the Unverified List (UL).[18]

In addition to the SDN List and proliferation sanctions notifications, providers must not conduct business with persons and entities on the DPL based on the EAR.[4] The DPL includes parties that have been denied export and reexport privileges.

In accordance with the EAR, exports to persons or entities on the EL require an export license.[4] [17] The EL contains a list of names of certain international persons—including businesses, research institutions, government and private organizations, individuals, and other types of legal persons—that are subject to specific license requirements for the export, reexport and/or transfer (in-country) of specified items. On an individual basis, the persons on the EL are subject to licensing requirements and policies supplemental to those found elsewhere in the EAR.

The presence of a party on the UL in a transaction is a "red flag" that should be resolved before proceeding with the transaction. [4] [18] The UL includes names and countries of foreign persons who in the past were parties to a transaction with respect to which BIS could not conduct a pre-license check (PLC) or a post-shipment verification (PSV) for reasons outside of the U.S. Government's control. Additional "red flags" can be found in Supplement No. 3 to Part 732 of the EAR.

To avoid violating U.S. laws and regulations, providers should consult these lists whenever an international customer places an order. Because the updated lists are available online, **providers should ensure they are using the most recently updated lists when screening customers or principal users against these lists.**

Additionally, U.S. persons or entities may not export, reexport, or transfer (in-country) an item subject to the EAR without a license if, at the time of export, reexport, or transfer (in-country) the exporter knows that the item will be used in the design, development, production, stockpiling, or use of biological weapons in or by any country or destination, worldwide.

If any of these checks reveals cause for concern, the provider should proceed according to the details provided in Section VII.

If an order involves an export, according to the EAR, both the provider and customer are required to maintain documentary evidence of the transaction and are prohibited from misrepresenting or concealing material facts in licensing processes and all export control documents.[4]

If *customer screening* raises any concerns, providers should conduct *follow-up screening.*

2. Sequence Screening

Providers should also perform *sequence screening.* The U.S. Government reminds providers to conduct *sequence screening* on orders from international customers to determine whether they are governed by and to ensure compliance with the EAR.[4]

The U.S. Government recommends that, in addition to screening for sequences unique to Select Agents and Toxins, providers use a "Best Match" approach to identify sequences unique to pathogens, toxins, and genetic elements on the CCL when an order is placed by an international customer. If the ordered dsDNA is controlled under ECCN 1C353 (which covers genetic elements and genetically modified organisms) and is capable of encoding a protein, an export license is necessary for all international orders, according to the EAR.[4] Because the EAR's CCL and the Select Agents and Toxins lists are not identical, it is recommended that providers ensure that international orders are screened to identify sequences unique to Select Agents and Toxins and CCL-listed items.

If a "sequence of concern" is identified, providers should conduct *follow-up screening.*

VII. Contacting the U.S. Government

In cases where *follow-up screening* cannot resolve an issue raised by either *customer screening* or *sequence screening*, the U.S. Government recommends that providers contact one of the following agencies for further information:

Federal Bureau of Investigation (FBI)

If an order raises concerns based on *customer screening* or *sequence screening* and *follow-up screening* does not sufficiently verify the customer's identity, the principal user's identity, and the order's intended end-use, providers should contact the Weapons of Mass Destruction (WMD) Coordinator at their nearest FBI Field Office. Providers should also contact the WMD Coordinator if *follow-up screening* reveals that the customer or principal user has no legitimate need for the order.

CDC and APHIS Select Agent Regulatory Programs (Select Agent Programs)

If necessary, the CDC and APHIS Select Agent regulatory programs can be contacted through the national Select Agent Web site (*http://www.selectagents.gov*). The CDC program can be contacted directly via e-mail at *lrsat@cdc.gov* or by fax at 404–718–2096. The APHIS program can be contacted directly via e-mail at *Agricultural.Select.Agent.Program@aphis.usda.gov* or by fax at 301–734–3652.

Department of Commerce

If *sequence screening* reveals that an order from an international customer contains a Select Agent or "sequence of concern," providers should contact the nearest field office of the Department of Commerce's Office of Export Enforcement. Providers should also contact the Office of Export Enforcement if they receive an international order from a country currently subject to a U.S. trade embargo or a customer or principal user that is on one of the proscribed lists described in Section VI. The Department of Commerce will contact other U.S. Government agencies as necessary. The supervisory office is in Washington, DC and the phone number is 202–482–1208. Locations and contact information for all field offices are available at *http://www.bis.doc.gov/about/programoffices.htm.* Assistance from an export counselor at the Department of Commerce is available by calling 202–482–4811.

[16] A general review of export control basics is available at *http://www.bis.doc.gov/licensing/exportingbasics.htm.*

[17] The Entity List is found in Supplement No. 4 to Part 744 of the EAR and can be found on the Web site *http://www.bis.doc.gov/entities/default.htm.* It is updated periodically.

[18] The Unverified List is found on the Web site *http://www.bis.doc.gov/enforcement/unverifiedlist/unverified_parties.html.* It is updated periodically.

Scenarios

If providers encounter one of the following scenarios and are unable to resolve issues raised by *customer screening* or *sequence screening,* they can contact one of the following U.S. Government agencies for assistance, using the contact information provided above:

1. Provider receives synthetic dsDNA order and a customer flag (suspicious customer) is identified in *customer screening. Follow-up screening* does not resolve the concerns. Recommend the provider contact the nearest FBI Field Office WMD Coordinator. FBI contacts other Departments and Agencies, as appropriate.

2. Provider receives a synthetic dsDNA order that is for a Select Agent or Toxin. Provider should refer to the Select Agent Regulations and follow necessary protocols. If necessary, the provider should contact the appropriate Select Agent Program (CDC or APHIS).

a. CDC or APHIS may contact FBIHQ as appropriate.

3. Provider receives a synthetic dsDNA order that incorporates a "sequence of concern;" *follow-up screening* reveals no legitimate purpose [11] for order or research requirement. Provider should contact the FBI WMD Coordinator. FBI contacts the CDC or APHIS as appropriate.

4. Provider receives an international synthetic dsDNA order incorporating a Select Agent or Toxin or a "sequence of concern" and DOC denies the export license. DOC contacts the FBI as appropriate.

5. Provider receives a synthetic dsDNA order from a customer that is listed on one or more restricted lists, which prohibits the fulfillment of the order. Provider should contact the FBI WMD Coordinator. FBI contacts DOC as appropriate.

VIII. Customer and Sequence Screening Software and Expertise

There are a variety software packages that can assist with the verification of customers (and principal users, if necessary) and screening against the necessary lists of proscribed entities. **Providers should be aware that commercially available software packages may not necessarily address all aspects of *customer screening* recommended by the U.S. Government.**

In addition to a sequence database and screening method, appropriate sequence screening software must be selected by providers of synthetic dsDNA. **The U.S. Government recommends that providers select a sequence screening software tool that utilizes a local sequence alignment technique;** a popular and publicly available suite of algorithms that meets this requirement is the BLAST family of tools, and other tools are available. BLAST is available for download for free at the National Center for Biotechnology Information Web site.[19] Similar tools are also freely or commercially available, or could be designed by the provider to meet their sequence screening needs. Specific criteria for the statistical significance of the hit (BLAST's e-values) or percent identity values will not be recommended because these details depend on the specific screening protocol. By utilizing the "Best Match" approach, the sequence with the greatest percent identity over each 66 amino acid or 200 bp fragment should be considered the "Best Match," regardless of the statistical significance or percent identity.

The U.S. Government recommends that providers of synthetic dsDNA 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. Such follow-up research could include comparing the ordered sequence to information found in the published literature about Select Agents and Toxins (or, when applicable, items on the CCL) or with information found in other databases of Select Agents and Toxins (or items on the CCL).

The U.S. Government recognizes that continued research and development on new and improved bioinformatics tools is desirable. As new methods are developed, U.S. Guidance may change accordingly.

IX. Records Retention

The U.S. Government recommends that providers:

- **Retain records of customer orders for at least eight years based on the statute of limitations set forth by U.S. Code of Federal Crimes and Procedures, Title 18 Section 3286.**[7]
- **Archive the following information: Customer information (point-of contact name, organization, address, and phone number), order sequence information (nucleotide sequences ordered, vector used), and order information (date placed and shipped, shipping address, and receiver name).**
- **Develop, maintain, and document protocols to determine if a sequence "hit" qualifies as a true "sequence of concern;" protocols that are no longer current should be maintained for at least eight years.**
- **Keep screening records of all "hits" for at least eight years, even if the order was deemed acceptable.**
- **Develop, maintain, and document their sequence screening protocols within company records; protocols that are no longer current should be maintained for at least eight years.**
- **Retain records of any *follow-up screening,* even if the order was ultimately filled, for at least eight years.**

If an order involves an export, according to the EAR, both the provider and customer are required to maintain documentary evidence of the transaction and are prohibited from misrepresenting or concealing material facts in licensing process and all export control documents.[4]

X. Appendix to *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*

Summary of Recommendations

The field of synthetic genomics is evolving rapidly. This document is intended to provide guidance to providers of synthetic double-stranded DNA (dsDNA) regarding the screening of orders so that they are filled in compliance with current U.S. regulations 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 recommends that all orders of synthetic dsDNA 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, providers of synthetic dsDNA:

(1) Gather the following information to verify a customer's identity:

- Customer's full name and contact information.
- Billing address and shipping address (if not the same).
- Customer's institutional or corporate affiliation (if applicable).

(2) Screen customers against several lists of proscribed entities (described in Section VI).

In cases where the customer is not affiliated with an institution or firm, the U.S. Government recommends that the provider conduct *follow-up screening.*

If a review of customer information reveals one or more "red flags,' the U.S. Government recommends that providers conduct *follow-up screening.*

[19] *http://blast.ncbi.nlm.nih.gov/Blast.cgi.*

Sequence Screening

The U.S. Government recommends that:

- Ordered sequences be screened using a "Best Match" approach to identify sequences that are unique to Select Agents and Toxins.
- For international orders, ordered sequences be screened using a "Best Match" approach to identify sequences that are unique to pathogens, toxins, and genetic elements on the Commerce Control List (CCL), in addition to screening for sequences that are unique to Select Agents and Toxins.
- 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 enable the detection of any "sequences of concern" in a dsDNA order.
- In order to ensure that "sequences of concern" embedded within larger sequences are not overlooked, when screening orders longer than 200 bps, providers should use screening techniques able to detect "sequences of concern" as short as 200 bps in length.

If a customer orders a synthetic dsDNA product that meets the definition of a Select Agent or Toxin,[20] domestic providers and customers must be in compliance with the CDC and APHIS Select Agent Regulations (42 CFR part 73, 7 CFR part 331, and 9 CFR part 121) in order to fill the order.

Follow-Up Screening

Providers should conduct *follow-up screening* if *sequence screening* or *customer screening* raises any concerns. In *follow-up screening,* the U.S. Government recommends that providers ask for information about the customer and principal user, including the proposed end-use of the order, to help assess the legitimacy of their order. Providers should gather the following information to verify a principal user's identity:

- Principal user's full name and contact information.
- Billing address and shipping address (if not the same).
- Principal user's institutional or corporate affiliation (if applicable).

If the customer or principal user is associated with an institution or firm, providers should contact the relevant biological safety officer, supervisor, lab director, director of research, or other relevant institutional representative to confirm the order, verify the customer's and principal user's identity, and verify the legitimacy of the order. If the customer or principal user is not affiliated with an institution or firm, providers should also conduct a literature review of the customer's or principal user's past research to verify his or her identity and the legitimacy of the order. If a literature review results in no publications, providers should request the unaffiliated customer or principal user provide references that can verify their identity and the legitimacy of the order. Additionally, providers should screen principal users against several lists of proscribed entities (described in Section VI), if this step wasn't already performed as part of *customer screening.*

Domestic Orders

The U.S. Government reminds providers of the following:

- According to U.S. regulations, no U.S. persons or entities may conduct transactions with individuals or entities on the list of Specially Designated Nationals and Blocked Persons (SDN List) without a license from the Department of the Treasury Office of Foreign Assets Control (OFAC).[21]
- According to U.S. regulations, no U.S. persons or entities may conduct business transactions with individuals sanctioned by the Department of State for engaging in proliferation activities.[22]

The U.S. Government recommends that providers check domestic customers against the most recent Department of Commerce Denied Persons List (DPL).[23]

In order to avoid violating U.S. law, providers are encouraged to check the customer against the most recent versions of these lists of proscribed entities before filling each order.

International Orders

The U.S. Government reminds providers of the following:

- All providers who export products from the United States to international customers must comply with the U.S. export laws, including the International Emergency Economic Powers Act (IEEPA),[24] the Trading with the Enemy Act,[25] and any implementing U.S. Government regulations or Presidential Executive Orders. Certain transactions with sanctioned countries may be permitted, but most require a license from OFAC and/or the Department of Commerce's Bureau of Industry and Security (BIS). Most transactions involving Cuba, Iran, and Sudan are prohibited. In order to comply with the U.S. export laws and regulations, providers must first determine whether a given transaction with a sanctioned country is permitted, and, if not permitted without a license or approval, obtain any appropriate export licenses or other U.S. Government permissions prior to exporting any product to sanctioned countries.
- According to U.S. regulations, no U.S. persons or entities may conduct business transactions with individuals and entities on the SDN List without a license from OFAC.[21]
- According to U.S. regulations, no U.S. persons or entities may conduct business transactions with individuals sanctioned by the Department of State for engaging in proliferation activities.[22]
- The Export Administration Regulations (EAR) require that providers have an export license from BIS prior to exporting a synthetic nucleic acid that is controlled by an Export Control Classification Number (ECCN) and is capable of encoding a protein.[23]
- U.S. persons or entities may not export, reexport, or transfer (in-country) an item subject to the EAR without a license if, at the time of export, reexport, or transfer (in-country) the exporter knows that the item will be used in the design, development, production, stockpiling, or use of biological weapons in or by any country or destination, worldwide.[23]
- In accordance with the EAR, providers must not conduct business with persons and entities on the DPL.[23]
- In accordance with the EAR, exports to persons or entities on the Entity List require an export license and are subject to licensing requirements and policies in addition to those elsewhere in the EAR.[26]

[20] Please see *http://www.selectagents.gov* to access the most recent Select Agents and Toxins lists. The CDC/APHIS national Select Agent registry Web site (*http://www.selectagents.gov*) contains a guidance document entitled "Applicability of the Select Agent Regulations to Issues of Synthetic Genomics" to assist providers in identifying synthetically derived Select Agent materials that would fall under the current regulations.

[21] Additional information, including the SDN List, is available at: *http://www.treas.gov/offices/enforcement/ofac/sdn/.*

[22] Announcements of such sanctions determinations are printed in the **Federal Register** and are maintained on the Department of State's Web site (*http://www.state.gov/t/isn/c15231.htm*).

[23] Visit *http://www.access.gpo.gov/bis/ear/ear_data.html* to access the most recent Commerce Control List and review the Export Administration Regulations.

[24] Visit *http://www.treas.gov/offices/enforcement/ofac/legal/statutes/ieepa.pdf* for additional information.

[25] Visit *http://www.treas.gov/offices/enforcement/ofac/legal/statutes/twea.pdf* for additional information.

[26] The Entity List is found in Supplement No. 4 to Part 744 of the EAR and can be found on the website *http://www.bis.doc.gov/entities/default.htm.* It is updated periodically.

• The presence of a party on the UL in a transaction is a "red flag" that should be resolved before proceeding with the transaction.[27]

• In accordance with the EAR, if an order involves an export, both the provider and customer are required to maintain documentary evidence of the transaction and are prohibited from misrepresenting or concealing material facts in licensing processes and all export control documents.[23]

In order to avoid violating U.S. laws and regulations, providers are encouraged to check the international customer against the most recent versions of these lists of proscribed entities before filling each order.

The U.S. Government recommends that providers utilize a "Best Match" approach to identify sequences unique to pathogens, toxins, and genetic elements on the Commerce Control List for international orders, as well as identifying sequences unique to Select Agent and Toxins.

Contacting the U.S. Government

In cases where *follow-up screening* cannot resolve concerns raised by either *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 as described in Section VII.

Customer and Sequence Screening Software and Expertise

Providers should be aware that commercially available customer screening software packages may not necessarily address all aspects of *customer screening* recommended by the U.S. Government.

The U.S. Government recommends that:

• Providers select a sequence screening software tool that utilizes a 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 records of customer orders for at least eight years based on the statute of limitations set forth by U.S. Code of Federal Crimes and Procedures, Title 18 Section 3286.[28]

• Archive the following information: customer information (point-of-contact name, organization, address, and phone number), order sequence information (nucleotide sequences ordered, vector used), and order information (date placed and shipped, shipping address, and receiver name).

• Develop, maintain, and document protocols to determine if a sequence "hit" qualifies as a true "sequence of concern;" protocols that are no longer current should be maintained for at least eight years.

• Keep screening records of all "hits" for at least eight years, even if the order was deemed acceptable.

• Develop, maintain, and document their sequence screening protocols within company records; protocols that are no longer current should be maintained for at least eight years.

• Retain records of any *follow-up screening,* even if the order was ultimately filled, for at least eight years.

Dated: October 6, 2010.

Kathleen Sebelius,

Secretary, U.S. Department of Health and Human Services.

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[27] The Unverified List is found on the Web site *http://www.bis.doc.gov/enforcement/unverifiedlist/unverified_parties.html.* It is updated periodically.

[28] Section 3286 specifies that no person shall be prosecuted, tried, or punished for any noncapital offense involving certain violations unless the indictment is found or the information is instituted within 8 years after the offense was committed. This statute of limitations applies to Title 18 Section 175(b) (possession of biological agents with no reasonable justification).

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

[60 Day–10–0666]

Proposed Data Collections Submitted for Public Comment and Recommendations

In compliance with the requirement of Section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995 for opportunity for public comment on proposed data collection projects, the Centers for Disease Control and Prevention (CDC) will publish periodic summaries of proposed projects. Alternatively, to obtain a copy of the data collection plans and instrument, call 404–639–5960 and send comments to Carol E. Walker, Acting CDC Reports Clearance Officer, 1600 Clifton Road NE., MS–D74, Atlanta, Georgia 30333; comments may also be sent by e-mail to *omb@cdc.gov.*

Comments are invited on (a) whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have a practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) ways to enhance the quality, utility, and clarify of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of information technology. Written comments should be received within 60 days of this notice.

Proposed Project

National Healthcare Safety Network (NHSN) (OMB No. 0920–0666 exp. 3/31/2012)—Revision—National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC).

Background and Brief Description

The National Healthcare Safety Network (NHSN) is a system designed to accumulate, exchange, and integrate relevant information and resources among private and public stakeholders to support local and national efforts to protect patients and to promote healthcare safety. Specifically, the data is used to determine the magnitude of various healthcare-associated adverse events and trends in the rates of these events among patients and healthcare workers with similar risks. The data will be used to detect changes in the epidemiology of adverse events resulting from new and current medical therapies and changing risks. The NHSN consists of four components: Patient Safety, Healthcare Personnel Safety, Biovigilance, and eSurveillance. In general, the data reported under the Patient Safety Component protocols are used to (1) determine the magnitude of the healthcare-associated adverse events under study, trends in the rates of the events, in the distribution of pathogens, and in the adherence to prevention practices, and (2) to detect changes in the epidemiology of adverse events resulting from new medical therapies and changing patient risks. Additionally, reported data will be used to describe the epidemiology of antimicrobial use and resistance and to understand the relationship of antimicrobial therapy to this growing problem. Under the Healthcare Personnel Safety Component protocols, data on events—both positive and adverse—are used to determine (1) the magnitude of adverse events in