Department of Health and Human Services

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

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 website: 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.[1] A list of "approved" customers is not practicable as it would have

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

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 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.