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Office of Medicine, Science, and Public Health
Office of the Assistant Secretary for Preparedness and Response,
FAO Jessica Tucker, Ph.D.
U.S. Department of Health and Human Services
330 C Street, SW., Room 5008B,
Washington, DC 20201

Comments for HHS from BIO on Screening Framework Guidance for Synthetic Double-Stranded DNA Providers

Dear Dr. Tucker,

BIO (Biotechnology Industry Organization) is the world's largest biotechnology organization, providing advocacy, business development and communications services for more than 1,200 members worldwide. Our mission is to be the champion of biotechnology and the advocate for our member organizations—both large and small. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology technologies. Corporate members range from entrepreneurial companies developing a first product to Fortune 100 multinationals. We also represent state and regional biotech associations, service providers to the industry and academic centers.

BIO is generally supportive of the referenced draft guidance and considers it an important initial step towards screening both producers and customers attempting to purchase double stranded (ds) DNA. BIO and its members recognize that developments in gene synthesis technology could result in synthetic DNA being deliberately misused by individuals and/or organizations with malicious intent. We welcome proportionate, risk and science-based measures that minimize both the risk of such misuse and any negative impacts on the conduct of research and business operations. BIO represents organizations that are end-users (customers) and producers of ds DNA; collectively those organizations have expressed concerns with regards to both sequence screening and customer screening. BIO offers the following comments on the draft guidance.

1. Further clarification on some of the screening framework and guidance that is not clear to us should engender more public discussion. Thus, we request an extension of two months for further public consideration and comment.

2. The guidance needs to organize and coordinate the sets of sequences that need to be screened against.

3. Currently, there are three separate lists of sequences to be screened against maintained by three different federal government departments/agencies (HHS/CDC/SAR, USDA/APHIS, and, for foreign orders, EAR's CCL). It would be helpful – especially for start-up companies – to centralize information and contact responsibilities.

4. The guidance suggests that a provider should search a given requested sequence, and if the "best match," of what the sequence is to a select agent, it raises a "red flag." The definition of "best

match," is a bit off, since in some cases a "best match," could be to a select agent, but still significantly different from the select agent. In other cases, there could be sequences that the 2nd, or 3rd, "match," was to a select agent, but it was 99% identical to the select agent. An agreement on a strict ID sequence identity cut off may be difficult to agree upon, but it might be more appropriate (i.e. if it is more than 90% identical to a select agent, should it be a "red flag"?).

5. The guidelines propose that customer screening applies for every order irrespective of the sequence and its potential to cause harm.

    a. The rationale for this appears to be at least in part due to the need for compliance with rules regarding US lists of proscribed and restricted entities.

    b. To the extent that this prevents acquisition by those with malevolent intent of sequences that may be harmful but are not associated with listed materials, this may be a positive measure.

    c. However, if this leads to significant delays or additional costs for sequences that are not harmful, it may be seen as unduly stringent and restrictive.

    d. It may also complicate attempts to accommodate these guidelines in a broader-based international framework which may be a desirable future development.

    e. The potential negative impacts may be minimized without compromising the aims indicated in the above "a," if the guidelines were amended to make clear that customer screening as a first step in the overall process need only address the relevant lists of proscribed and restricted entities.

6. There should be some consideration of how that identity is distributed. If a given 200 nt (nucleotide) gene sequence is identical to a select agent for 100 nt, then totally different for the next 100 nt, it is probably more concerning than if every other nucleotide is a match.

7. Other more general concerns expressed: are all of the select agents on the list fully sequenced? If the sequences to all the agents are not in the databases, they will not come up as "best matches," even if they are exact matches.

8. This document indicates that oligonucleotides smaller than 200 base pairs in length are excluded from scope. This provision will be considered by some to be overly restrictive and by others of not going far enough. It would probably be prohibitively complex to extend this to single stranded oligomer (oligo) providers, so the restriction to ds DNA of >200 bps (base pair sequence) is understandable. However, it is really a very simple matter to convert the single stranded oligos to double stranded longer length DNA; so if a toxin were desired, but genes were being screened, some oligos could be ordered instead. Some listed toxins for example may be encoded by sequences not more than just twice this length. For example, a recent paper in the scientific literature (D. G. Gibson Nucleic Acids Research, 2009, Vol. 37, No. 20 6984–6990) demonstrated that the yeast *Saccharomyces cerevisiae* can take up and assemble at least overlapping single-stranded oligonucleotides (60 nucleotides in length and with 30 nucleotide overlaps) and a linear double-stranded vector in one transformation event, a process that provides a "straightforward scheme for assembling chemically-synthesized oligonucleotides" that "could be a useful tool for building synthetic DNA molecules". The rationale for the 200 base pair cut-off appears to be that the guidance is targeted at gene synthesis and not oligonucleotide providers. While recognizing that nothing which allows essential legitimate work to progress can completely prevent the risk of misuse, it is perhaps worth questioning whether this rationale is sufficient justification on its own.

9. The guidelines refer to archiving requirements related to sequence and customer information. This is not contentious for orders based on contractual arrangements between a supplier and a customer that provide for protection of intellectual property and other commercially sensitive information. Arguments, however, have been advanced that risk mitigation may be improved by aggregating information, so that all providers may be able to access this information. If proposals for aggregation are to be considered further we believe that careful consideration should be given to the protection of information for which confidentiality can be clearly justified.

10. One of the customer "red flags" identified in the document is associated with requests from customers for unusual labelling or shipping procedures (e.g. requests to misidentify the goods on the packaging). While the example provided appears to be sensible in the context of a "red flag," not all specific labelling requests would be. For example, customers may, in the interests of security, wish to include specific indications on a package to ensure that delivery to the end-user identifies the nature of the contents to those with a need to know, while at the same time avoiding undue advertising of the package contents to those who might wish to subvert delivery for malicious purposes. It may be helpful if recognition of legitimate labelling requests that would not signal a "red flag" could be included in the final document.

11. The indicator that large volume orders should be considered "red flags" does not provide automatic protection. Once you have a gene it is pretty standard molecular biology to make lots more of it. It does not hurt to keep it on the books for 8 years (stipulated in the document) as something to check for, but it seems unlikely that it would be seen.

12. In addition to the foregoing substantive issues, we would also draw attention to the construction of the text in Section IV of the guidance where the overall screening methodology is set out in 3 sequential steps as follows: 1. Customer screening to check for any "red flags;" 2. If no "red flags" are apparent, screening of the requested sequence and follow up of "matches"; 3. End-use checks if concerns arise during either customer or sequence screening. As written this implies that no sequence screening is required if a "red flag" arises during customer screening. This appears inconsistent with the intent of the document and with other sections

BIO is appreciative of the opportunity to submit comments and would be pleased to engage further in the ongoing interagency process developing the guidance.

Sincerely,

Brent Erickson
Executive Vice President
Biotechnology Industry Organization