

Comments of the International Council for the Life Sciences on the DHHS' Screening Framework Guidance for Synthetic Double-Stranded DNA Providers.

To Whom It May Concern:

On behalf of the International Council for the Life Sciences (ICLS), we should like to thank you for the opportunity to comment on the draft 'Screening Framework Guidance for Synthetic Double-Stranded DNA Providers' (the Guidance).

The ICLS believes the Guidance represents an important contribution by the US Government to the debate on how best to facilitate beneficial advances in the nascent field of synthetic biology by addressing ways to restrict the potential of various players to misuse the technology for nefarious purposes.

A first, general, point derives from the fact that pursuant to the producers of synthetic genomic products (the Producers) of the recommendations the Guidance is intended to be voluntary. Given that the Guidance is, then, exhortatory rather than mandatory, the ICLS considers that the Guidance should throughout exhort Producers to follow industry best standards, rather than recommend lowest common denominator procedures.

For the most part, the Guidance does indeed recommend adoption of best industry practice. But in two, specific areas (both related to the screening of orders), it appears to adopt the lowest common denominator:

1. Identification of sequences of concern
2. Sequence screening methodology

With regards to the Identification of sequences of concern, the Guidance recommends that

‘nucleic acid sequences be screened for nucleic acids derived from or encoding Select Agents and Toxins and, for foreign orders, for nucleic acids derived from or encoding pathogens on the Commerce Control List’.

However, this appears to be a minimalist standard in comparison to the current practice for gene sequence screening adopted by the International Gene Synthesis Consortium (IGSC), which calls for companies to

‘screen the complete DNA sequence of every synthetic gene order against the DNA sequences in a Regulated Pathogen Database, and against all entries found in one or more of the internationally coordinated sequence reference databanks (i.e., NCBI/GenBank, EBI/EMBL, or DDBJ).’

The IGSC envisage that the Regulated Pathogen Database will be compiled and updated by its members and

‘will include data from all organisms on the Select Agent list, the Australia Group List, and ***any other national list of regulated pathogens***’ [emphasis added].

The International Association Synthetic Biology (IASB) adopts a very similar, but even more extensive, method for determining sequences of concern:

‘DNA sequences submitted as inquiries or orders for DNA synthesis by customers will be screened against GENBANK for reasonable sequence similarity to pathogens. Members may take further

reasonable steps to determine the function and evaluate the biorisk associated with homologous genes ...’

The ICLS accordingly would advocate that the Guidance be amended in Section V.B.1. (and elsewhere as necessary) to reflect the best industry standard of screening against the industry’s Regulated Pathogen Database and one or more of the internationally coordinated sequence reference databanks, and that Producers also take further reasonable steps to determine the function and evaluate the biorisk associated with homologous genes.

With regard to sequence screening methodology, the Guidance notes that

‘the US Government considered two distinct screening approaches, one based on a curated database of known sequences of concern and another utilizing a method called “Best Match”. The first approach requires the creation of databases identifying specific features such as known virulence factors, house-keeping genes, etc. While the acquisition of such knowledge is progressing, at this time customized database approaches are unable to provide a robust solution that can be implemented by DNA synthesis providers. Consequently, the US Government recommends a “Best Match” approach for sequence screening. In this approach, a query sequence is deemed to be unique to a Select Agent or Toxin if the sequence (amino acid) is more closely related to a Select Agent or Toxin sequence than to a non-Select Agent or Toxin sequence. Sequences that are equally related to both a Select Agent or Toxin and a non-Select Agent or Toxin will not produce a sequence hit. As a result, the number of hits for sequences that can be obtained from non-Select Agents and Toxins will be reduced.’

In this regard, the ICLS would note that the IASB proposal that Producers additionally should ‘take further reasonable steps to determine the function and

evaluate the biorisk associated with homologous genes' represents a more robust approach for two reasons:

1. it would capture gene sequences of concern which are not captured by the Best Match approach
2. it would lead to a far more dynamic and up-to-date list of sequences of concern against which to screen orders, in that the results of each investigation into an order for a gene sequence which is not in the database will be added to the database immediately upon completion of the database.

Furthermore, the ICLS does not consider that the US Government's stated reason for adopting the "Best Match" approach over the 'curated database of know sequences of concern' flows logically. While the curated database may not yet, or ever, represent a complete listing of sequences which should be of concern, it already represents an advance over the "Best Match" approach, which is limited to a subset of the sequences of Select Agents and Toxins.

Given that the ICLS considers both that the 'curated database' represents an immediate improvement upon the Best Match approach, and that it offers more rapid acquisition and sharing of data about new sequences of concern and so offers the prospect of better security sooner, the ICLS strongly urges the US government to amend Section V.B.3. of the Guidance (and elsewhere as necessary) to recommend that Producers use the 'curated database' or 'homologous gene' approach for screening orders.

It is very important at this stage that the US Government does not undermine the efforts currently underway by the synthetic biology industry to coalesce around a set of standards for how to screen customers and orders responsibly. Both the IGSC and the IASB have set standards for inclusion in the list of sequences of concern and for screening methodology which are higher than those proposed in the Guidance.

The ICLS is concerned that, if the US Government sets standards in these two areas which are lower than the industry itself is trying to adopt as the industry standard, those Producers who have not yet signed up to either the IGSC or the IASB standards will fail to see why they should do any more than the lower US Government standard, and that this in turn will result in both the IGSC and IASB standards failing over time as members defect to the lower, and less onerous, standards of the Guidance. Consequently, the ICLS considers the future prospects of the industry coalescing around one, higher and more rapidly adaptable standard will be significantly undermined unless the US Government amends the sections of the Guidance as suggested above.

The ICLS approves the inclusion in the Guidance of the idea that Producers should not grant customers unusual levels of confidentiality. The ICLS would suggest that Section V.A.2 of the Guidance might be amended to recommend that Producers should not afford customers levels of confidentiality which would inhibit the Producers' ability to screen customers and orders in line with best industry practice.

Finally, the ICLS would like to identify itself with and support the observations submitted by the International Association Synthetic Biology (IASB).

Once again, thank you for the privilege of being able to comment on the draft Guidance.

Yours sincerely,

Terence Taylor, President
Tim Trevan, Executive Director
International Council for the Life Sciences
Suite 625, 4245 Fairfax Drive, Arlington, VA