American Society of Gene + Cell Therapy

June 29, 2022

Re: ASGCT's comments on proposed revisions to the federal Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

Dear Sir/Madam:

Our organization appreciates the opportunity to comment on this review and revision process for the "Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides" ("the revised guidance"). We are a nonprofit professional membership organization comprised of scientists, physicians, clinicians, and other professionals working in gene and cell therapy in settings such as universities, hospitals, and biotechnology companies.

Many of our members have spent their careers in this field performing the underlying research that has led to today's robust pipeline of transformative therapies. By bringing together members from diverse backgrounds, our organization strives to be a catalyst for transformative medicine using genetic and cellular therapies to control and cure human disease. We appreciate HHS' ongoing willingness to hear from stakeholders about ways to improve and adapt policies to address the unique and evolving nature of synthetic oligonucleotide technologies.

We believe that the original guidance was appropriate for the time in which it was written. And with the advance of nucleic acid synthesis technologies in the intervening decade, we agree that it is appropriate to update the guidance now. Generally, there are many areas of the revised guidance that are reasonable and fitting; other suggested changes, we believe, would offer little added value to the field or would be actively challenging for both provider and customer to implement. Our comments below are organized to address the five major identified areas in which changes have been proposed, highlighting both the changes we support and those where we have concerns.

1. *Expanding the definition of sequences of concern beyond the sequences unique to agents on the select agents and toxins list and Commerce Control List.*

We believe it is entirely appropriate that new agents should be added to the select agents and toxins list (SATL) and Commerce

Control List (CCL) and be subject to screening as they are identified and as the hazard potential becomes apparent. The universe of such agents will continue to grow and evolve. To ensure that screening entities are able to keep up with that growth and support efforts to prevent misuse, our organization would like HHS to consider the creation of a single official list that includes full sequences of concern, not only names, which can serve as a centralized, curated source of truth.

The current system requires that a screening organization first consult the SATL and the CCL, then search one of several public databases to determine the precise sequence they are looking for. In our members' experience, there are over 60 million entries in public databases relating to the names included on the CCL. Entries in such databases may contain errors or ambiguities, which can result in delays or rejection of an order until the source of inaccuracy is identified and resolved. We would therefore support creation of a list of sequences housed and maintained 2 under one government agency, in collaboration with other relevant agencies as appropriate, which would be a useful reference for all parties responsible for screening.

We do recognize that there may be security considerations if the SATL and CCL are paired directly with the corresponding genetic sequences for those agents and toxins. If that is the case, we would like to generally advocate for adjustments to the current system that would relieve some of the burden on legitimate actors, as HHS may deem appropriate.

2. *Expanding the scope of the guidance to include both single and double-stranded forms of both DNA and RNA.*

In the Definitions section of this revised guidance, "Synthetic oligonucleotides subject to screening" includes "DNA or RNA, single- or double-stranded, of lengths 50 base pairs (bp) or longer if ordered in quantities of less than one micromole, or lengths of 20 bp or longer if ordered in quantities of one micromole or greater."

Similarly to the prior question, we believe broadly that the changes to this portion of the guidance are reasonable and appropriate. We have however identified a few points of concern.

The ability to produce long double-stranded (ds) DNAs (i.e., synthetic genes) from shorter component synthetic single-stranded (ss) oligonucleotides has steadily progressed, so our organization agrees that it makes sense today to additionally screen ssDNAs (i.e., gene building blocks). It further makes sense to screen shorter DNA sequences (50 bases or longer in the revised guidance) than earlier longer limits (200 bases for dsDNA in the original guidance). Computational power and algorithms have steadily improved over recent years and it would not be a significant burden on providers to perform such screening, particularly if approaches other than BLAST are employed, which is more computationally intensive than some other approaches.

On the other hand, we do not agree that screening RNAs within this reduced length range will enhance biosecurity. Long ssRNA can function as mRNA, so could in theory be used in hazardous ways and therefore could be of value to screen. Short ssRNAs, however, are not

readily used as building blocks for stepwise ligation or amplification-based methods of gene assembly. We believe that screening such ssRNA is therefore unnecessary, and respectfully recommend that it should be removed from this guidance.

In general, our organization has concerns that screening oligonucleotides, DNA or RNA, of length 20 (which comprise 6 different reading frames for 6 amino acids residues) would present a significant burden to providers. At that level of screening, it would be very common to turn up a large number of homologies leading to false positive identifications, requiring customer orders to be frequently put on hold pending resolution of the finding. That additional follow-up would add significant regulatory burden to the provider and risk delays that, if they became too common, may push some customers to seek materials from companies that do not follow this voluntary guidance at all.

We also do not agree with the assertion that oligonucleotides ordered at 1 micromole scale or larger are deserving of special scrutiny. Large scale oligonucleotides are typically ordered when a single short primer is needed to perform repetitive tasks, such as PCR reactions for widespread Covid testing. For the majority of users, only attomole or femtomole amounts of oligonucleotides are typically needed for assembly today; possession of a larger quantity does 3 not in itself indicate or facilitate nefarious intent. We therefore respectfully suggest that the reference to 20 bp screening in this revised guidance be removed altogether.

3. *Reducing the burden on synthetic oligonucleotide providers by recommending that customers preemptively provide information to verify their legitimacy when ordering synthetic oligonucleotides that they know contain sequences of concern.*

We believe broadly that these new recommendations would be useful, though our members' experience in the industry suggests customers may be unlikely to provide the suggested information. Particularly given the prevalence of centralized purchasing departments for academic institutions and industry organizations, the person placing the order may not be in a position to explain the underlying reason for the purchase. Additionally, echoing our concerns in the previous section, if providers are asked to screen at 20 bp the likelihood of homologies is high and the customer is unlikely to put in the effort upfront to identify all of those possibilities and include it in their order information. In summary, while we support the spirit of this recommendation, we question its ultimate utility under real world ordering conditions.

4. *Expanding the scope of the Revised Guidance to include recommendations for customers, principal users, and end users.*

We broadly agree with these changes and have no specific comments.

5. *Providing best practices to manufacturers of benchtop oligonucleotide synthesis equipment.*

Our organization understands the intent behind these changes to the revised guidance, but again we respectfully question whether the application in real-world settings will be effective. Once a benchtop synthesizer has been delivered to the customer, there is effectively no way to regulate what sequences are made on it. At this time the primary impediment to making your own oligonucleotides is handling the necessary organic chemistry reagents, which is highly complex and comparatively expensive to procure the quantities needed for individual use (as opposed to use at a dedicated oligonucleotide manufacturer). However, new enzymatic methods of oligonucleotide production are under development, with the goal of building benchtop synthesizers which would require far less expertise to use. At the point the machines are more common and being accessed by additional individuals, regulation becomes increasingly difficult. In a similar vein to our concerns under item #3 above, legitimate researchers and institutions may have complex purchasing and use arrangements that would make it extremely difficult for manufacturers of synthesizers to confirm and continuously track the end user's intent.

Thank you for your consideration of these comments.