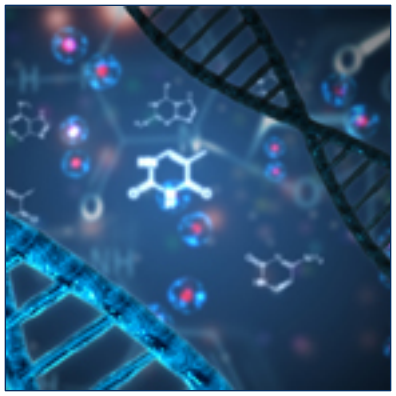
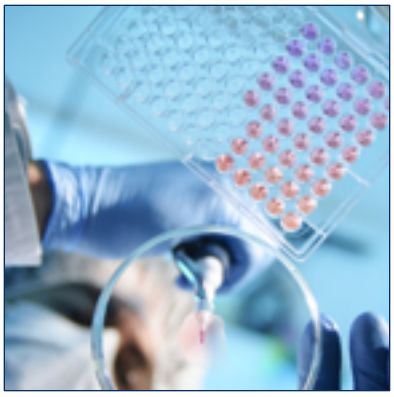
U.S. Department of Health & Human Services

Office of the Assistant Secretary for Preparedness & Response

Responses to *Federal Register Notice, Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides*



ASPR



aspr.hhs.gov

Responses to Federal Register Notice, *Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides*

1. The Athena Agenda: Advancing The Apollo Program for Biodefense, in its April 2022 report, provides Many recommendations and considerations for companies providing oligos. In addition should there be any control around purchasing DNA printers? Any owner wouldn't need to purchase oligos since they would simply be printed in the lab using GENBANK sequences. (Federal Government)
2. Hello, I think it will be useful to trace projects after screening. The production of pathogens and bioweapons must come to a halt. That can no longer be something "lucrative." Because in the big picture it's really not, and obviously has serious consequences that supersede humanity. Thank you. (Academia)
3. Please consider also limiting the ability to purchase nucleotides that can be used on DNA synthesis instruments. If the instruments and the nucleotides fall into the wrong hands, any regulation of oligomers is moot. (Federal Government)
4. In looking at the part about benchtop synthesizers, if manufacturers design an innate mechanism to screen sequences, how would they go about that? Is it the manufacturer of the owner that is responsible for the continuous screening of sequences which are synthesized? Once a synthesizer is provided to someone that the manufacturer deemed legitimate, what are the mechanisms for screening against SOCs? Who do the machines report to if it is flagged that an SOC is being synthesized? I would argue that providers of these machines ought to be required to implement some of these measures into the machines. Perhaps not are all necessary, but data logging and forced user authentication should not be optional components for providers of benchtop synthesizers. (Federal Government)
5. As someone with three decade of experience working in biosecurity and defense in equipment-intensive laboratory research, as well as extensive bioinformatics experience, the following proposed requirement needs to be rejected because it is impractical and would lead to increased cyber vulnerabilty: • Manufacturers should provide the capability into their oligonucleotide synthesizers to enable secure internet connectivity to screen sequences for SOCs and to authenticate legitimate users.[7] Manufacturers are also encouraged to include a data logging function to maintain a record of the oligos

synthesized on the equipment. Furthermore, Manufacturers should develop a mechanism to authenticate the user of these equipment before synthesizing oligonucleotides containing SOCs. First of all, like most of this guidance, it should be considered in the light of this fact: there is a large installed base of equipment that does not have this feature. Therefore this recommendation, which has multiple security problems and operational implementation problems (see below), provides no actual protection against any adversary who would want to get access to an existing platform that does not have this built-in audit mechanism. So it has little real advantage in deterring even a mildly determined adversary with enough means to purchase and run a used oligo synthesizer. It does create a large vulnerability towards adversaries with only minor cyber skills, because the stipulation of a "secure" internet connection will be impossible to achieve without large expenditures. The recommendation seems to have been written without a knowledge of the difficulties of actually using networked instruments in real-world conditions. The idea that instrument would only allow synthesis if your input sequence was checked over the internet first falls in like with the (unfortunate) tendency of instrument manufacturers to want to maintain internet connection and often considerable data access and control over instruments that their users buy and install. Practically however, manufacturers almost never provide “secure” internet access because they don’t keep the OS they run up to date on the embedded or attached computers that run the instrument. Here is the issue: Instruments without secure operating systems should be forbidden to be connected to the internet. The instrument must therefore have a secure operating system. Versions of windows, mac OS or linux are constantly being upgraded to patch security problems. (At our national lab, only a handful of OS versions are allowed to be connected to the internet because of this problem). The software that runs the hardware and data processing almost always sits on top of one of the standard operating systems that is running the embedded or attached computer that runs the instrument. Instrument companies do not write their own operating systems or make their own computers. Instrument manufacturers are notoriously slow to upgrade the base operating systems for their embedded computers, because every time the base OS is upgraded they risk having to rewrite the software that runs the hardware and does the data processing (they at least have to do a thorough revalidation). An example is Illumina sequencers: we cannot them to our networks until they get their next software version out- a process that takes months/years. Constantly upgrading or revalidating software every time the base

windows or linux OS gets a new version is generally not an economically competitive proposition especially for a small company. Simply insisting on it with the above ill-considered recommendation is not going to make the economic reality go away. Without the OS being secure, the instruments cannot be mandated to maintain internet connectivity just to be operational, which would be an implication of the requirement, while at the same time being "secure". Once the possibility is admitted that the OS running the instruments is unlikely to be up to date or secure, even for a fraction of the fleet of instruments, the idea that the instrument has an onboard database or even worse accesses a centralized database of sequences becomes a huge security problem, not a solution, since an adversary can access this data, and not only use it for industrial espionage, but even use it for information to evade assays and countermeasures. (NGO)

6. Overall, we applaud the decisions reflected in the draft updated screening framework guidance. In particular, we believe the following decisions are highly valuable for increased biosecurity: - Expanding the parties responsible beyond providers to all persons and organizations who work with or transfer sequences of concern - Extension from dsDNA to ssDNA and RNA. - Reduction from 200bp to 50bp for minimum length to screen - Explicit support for methods other than BLAST We believe that there are two points on which the current guidance requires additional clarification, however. 1) As currently written, the definition of “sequence of concern” is ambiguous. It could be interpreted to mean that everything with ANY pathogenic or toxic potential should be treated as being a sequence of concern. This will be a major problem for organizations that want to comply with the recommendations, since that definition is overly broad and will include many pathogens and toxins that are frankly not actually concerning. We believe a better approach would be to say something like: “An organization should define and document its criteria for determining whether a sequence is of concern. At a minimum, sequences of concern must include sequences derived from or encoding select agents and toxins or items on the CCL, except when also found in unregulated organisms. Sequences of concern may also be expanded to include other classes of sequences that an organization judges to be of concern, on the basis of their ability to produce concerning effects with regards to toxicity or pathogenicity.” 2) The endorsement of non-BLAST methods is separated from the endorsement of BLAST and the two are written in a potentially contradictory manner. Instead of “This Revised Guidance recommends that providers use a local sequence alignment technique, such

as the BLAST family of tools." and then in the next column "Providers may also choose to use other screening approaches that they assess to be equivalent or superior to the Best Match approach or supplement it," we would recommend instead writing "This Revised Guidance recommends that providers use either Best Match with a local sequence alignment technique (such as the BLAST family of tools) or another screening approach that they assess to be equivalent or superior to the Best Match approach." There are also two points on which we disagree with the current draft: 1) It is not appropriate to adjust screening criteria based on the number of moles ordered. Even very small amounts of DNA can be readily amplified after an initial assembly stage. Thus, if short sequences are of concern, they are of concern even in low quantities. 2) At the same time, we believe that a 20 bp minimum is too short a target for screening. With both current and near-term accessible technology, it is difficult to assemble gene-scale sequences from fragments less then 40 bp in length. At the same time, a vast number of primers are in the 20-30bp range, and would greatly increase the burden of compliance. Thus, any length less than 30bp is certainly a poor cost/benefit tradeoff, and we see little benefit in going below 40 bp. (Industry)

7. My chief concern is that this revised guidance remains solely focused on industrial or benchtop synthesis of oligos. This ignores the fact that whole genome editing technologies are now on-market (e.g., Inscripta's Onyx) and the high likelihood that the future end state of synthesis technology will be whole-genome writing at the benchtop. Current oligo synthesis technology screening is inherently context-free: the entity desiring to do screening typically does not know the intended use of the oligos being ordered. Companies (and academia) are loathe to disclose details for IP reasons. Hence, when asked they can reply with vague answers such as "for vaccine research" or "testing diagnostic assays", etc. In contrast, whole genome editing has an inherent context: the end-user is ordering a library of desired edits that will be applied to their desired base strain(s) with a goal of finding edits that optimize some phenotypic aspect (e.g., enzymatic output, survival under specific stress(es), etc.) The provider of whole genome editing technology can only truly determine potential biosecurity/biosafety risk if sufficient genomic context is provided. For example, assume that a customer is ordering a library of edits targeting one gene that is best known for being part of a multi-gene virulence cassette in microbial organism X. Absent knowledge of the genomic context, a screening red flag certainly should be raised for this "sequence of concern" because it might result in a gain of function (e.g., increased lethality, transmissibility, etc.) We would

expect this to be the case for traditional context-free synthesis providers. However, consider the difference for a genome editing provider, who also has been provided the sequence of the customer's base strain(s) upon which the edits will be applied. If the base strain(s) are not from organism X and if the other gene(s) from the known virulence cassette are not present in the base strain, the screening software could determine that a red flag was not warranted since the presence of this single heterologous gene could not cause the known virulence found in organism X. As many microbial genes play multiple roles in different pathways, the genome editing provider's screening software could avoid issuing a "false alarm" that would otherwise consume expensive human review effort. (It is worth noting that genome editing customers who refuse to provide sufficient base strain contextual information will suffer the same high false alarm rate as a traditional synthesis order for oligos from the same gene.) Clearly, the likely end-state of technologies capable of writing whole genomes will by definition provide the contextual information needed to make high-quality screening decisions, limited only by our knowledge of the roles that genes play in all the pathways in which they participate. Thank you for considering this plea to widen the scope of the revised guidance to at least acknowledge the nascent whole genome editing technologies and the likely future whole genome writing technologies. While it may be too much to think of requiring traditional synthesis customers to provide genomic context for each oligo ordered, please recognize that the genomic manipulation technologies that go past simple synthesis have an essential need for genomic context to properly determine the risk of customer orders. (Industry)

8. Under the revised guidance, “sequences that contribute to toxicity or pathogenicity” are considered sequences of concern (SoCs) that are covered by the guidance even if these are not encoded by a regulated biological agent. 'Pathogenicity' and 'toxicity' are ambiguous terms Parasites are limited in the taxa they affect. Parasites typically have a narrow range of organisms they are capable of parasitizing. Bad bugs are not universally bad. This is because these microbes encode specific sequences that can interact with molecules of susceptible hosts—but NOT other organisms. To generate an appropriate list of SoCs, one first needs to formulate a list of host taxa of concern, because this list of important host taxa conditions the list of parasites from which SoCs will be selected. 1) SoCs from human parasites: Fewer than 2000 species of bacteria, viruses, fungi, worms, and protozoan parasites can produce a disease state in a human. Excluding immune-compromised humans drops the list of ‘bad bugs’ to ~1000. These organisms

encode sequences that enable them to resist host immune defenses, damage the host, adhere to host tissues, invade host cells, and disseminate across the body. They also do other deleterious things, but those features are the 'worst' (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9119117/). 2) SoCs from parasites of human livestock: The government may decide that sequences from parasites that plague cows, pigs, turkey, chickens, sheep, and goats should be on an approved list of sequences of concern, but that sequences from parasites that (only) affect oysters, shrimp, trout, salmon, or tilapia should not be. 3) SoCs from parasites of human crops: Similarly, it could be decided that disease agents of corn and cereal grains—which supply a whopping percentage of the calories consumed by humans and their livestock—should be considered when looking for SoCs, but not parasites of fruits or vegetables. 4) Deciding what target taxa are important: If the SoC approach is taken, then experts from within USDA, DHSS, perhaps CDC and other agencies, as well as outside experts in infectious diseases should be involved in formulating lists of (i) important host taxa and (ii) parasites affecting those taxa from which SoCs will be documented. It appears that SoCs are present in all microbes that can cause disease in host species so the bulk of the work for the government should simply be deciding which host taxa to pick. Then the research enterprise will reveal what SoCs should be selected—the list of SoCs cannot be determined a priori (without reference to the voluminous literature in microbial pathogenesis). Then some entity should be assigned to collect and compile the relevant data for the official SoC list. There are several datasets of which we are aware that would be useful to include in such a list. Encoded biological toxins are usually broader in the number of taxa they can affect than parasites. To be effective, a toxin must have access to the target process it can affect. 1. Encoded animal venom components are usually single components. They don't have a delivery subunit that mediates transit across a physiological barrier in the target taxa. Instead, they rely on breaching of host barriers by their delivery mechanism, whether stinger, fang, or nematocyst. The injected venom components then have access to their targets which are always on the external side of cell membranes, tissues, and organs. Sometimes blood components are affected. 2. Plant toxins are almost always delivered by ingestion. They typically consist of at least two components, a toxic component that administers the biochemical insult within a cell and a delivery component that mediates transit across the cell membrane or across tissue barriers. One class of plant toxins inactivate animal ribosomes (ribosomal inactivating proteins) by cutting a glycosidic

linkage in an essential RNA. The (toxic) enzymatic subunits are present in most cereal grains, but they do no harm because they lack a delivery subunit. But similar subunits form the basis for the toxic activity of ricin, abrin, and mistletoe toxins because they possess a second delivery component that adheres to target cells and mediates the translocation of the toxic protein across the cell membrane. Only the combination of toxic component and delivery component is effective. 3. Toxins not toxic for taxa humans care about shouldn't be included in lists of SoCs: Biological databases hold thousands of sequences of 'toxin/antitoxin' sequences. These entities are control modules by which plasmid 'parasites' maintain themselves within their bacterial hosts. They are very potent toxins that are quite pathogenic, but only for bacteria. Sequences of concern are not equally bad, but how might they be reported so that these differences are addressed? As discussed above, the terms invoked by the new regulations, "toxicity" and "pathogenicity" are not easily parsed, even by experts. Close to 300000 sequences in UniProt have been tagged with the gene ontology term GO:0009405 (pathogenesis). The rationale for the tag is inexplicable for most sequences. So how should one conceive of pathogenicity? Some have attempted to define SoCs involved in pathogenesis at the molecular level based on the published literature (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9119117/). They categorize SoCs according to whether they act DIRECTLY on a host/target molecule or INDIRECTLY. Some contract researchers have developed a compact controlled vocabulary of ~32 terms, functions of sequences of concern (FunSoCs), to describe the affect these SoCs have on host organismal and cellular biology. In a parallel effort, a group at Johns Hopkins Applied Physics Laboratory (JHU APL) developed terms for a discrete ontology of about ~170 terms that describe the types of molecular interactions particular to pathogenesis. FunSoCs and PathGO are descriptive tools for SoCs that allow their hazards to be BOTH understood by experts AND identified by software. A system of numerical weights with custom analysis software could be used to provide a crude ranking of individual sequences as biothreats. The working assumption is that sequences that have more capacities to subvert host immune function or damage host biology are more concerning than those with fewer such capacities. Sequences that act INDIRECTLY in pathogenesis DO NOT NEED to be included in official lists of SoCs. Sequences that act indirectly do not target host cell molecules but rather work on molecules of the parasite. While they can pose a risk, it is not as great as those that operate by directly manipulating host targets. That said, not all direct-acting SoCs need

to be included in official lists of sequences of concern. Not all direct-acting SoCs are equally problematic if one is considering threat scenarios that involve bioengineering/gain-of-function. We think the primary worries are SoCs that are: 1) Damaging 2) Subvert the host immune system 3) Mediate adhesion to the host 4) Promote Invasion of host cells 5) Enable dissemination in the host Sequences that enable movement in a host cell, absent another function of concern such as dissemination, are not that dangerous. Similarly, sequences that are involved in the construction or maintenance of a replicative niche within a host cell are not as dangerous as those that subvert immunity. The process of building a replicative niche for a bacterium such as Legionella pneumophila within a host macrophage or Shigella in an enterocyte can involve hundreds of sequences. What data should be included in a 'list' of SoCs? Should it be an open list of sequence names? Or a list of sequence names with accession numbers? Or a list of names, accession numbers and a tabular list of problematic features (damage, immune-subverting, etc)? Should terse but specific descriptions of pathogenic activity such as those of PathGO or FunSoCs be associated with each SoC? Should detailed information regarding host targets be included with the list Should references to the literature be associated with each description of pathogenic function? Who should have access to lists of SoCs? 1) Should the list be publicly available to the scientific community at large? 2) Should institutional review entities responsible for implementing DURC oversight of research conducted at their institution have access to this information? 3) Should access to such a list be limited to USG agencies that fund potential DURC research such as NIH and CDC? 4) Should different groups have access to different lists? Our opinion is that a "complete" list of SoCs with (i) names of sequences, (ii) accession numbers, (iii) tabular lists of problematic features, (iv) FunSoCs, (v) PathGO terms, (vi) detailed features of what host cellular and molecular systems are affected including the specific host proteins targeted and (vii) references from which the assertions are derived should be limited to just a few groups. Such a dataset represents a high level of information hazard by compilation if one is concerned with malicious bioengineering. Lists that include just the (i) names of sequences, (ii) accession numbers, and (iii) tabular lists of problematic features should be available to DNA synthesis companies, and perhaps other commercial vendors for screening purposes. Vetting such a list of SoCs (QA/QC), keeping it updated, and issuing/versioning it appropriately are topics that relevant SMEs in data curation,

bioinformatics, infectious diseases, biodefense, and policy are going to need to hash out. (Industry)

9. The comments below are a combined response from both academic and industry respondents. To begin, we would like to state that we support the two parallel goals for the Revised Guidance, i.e., minimize the risk that individuals with malicious intent will use nucleic acid synthesis technologies to 1) produce pathogens or toxins regulated by the FSAP and CCL (henceforth “controlled SoCs”) and 2) create novel high-risk pathogens or toxins using sequences from unregulated organisms (henceforth “uncontrolled SoCs”. We believe that the draft Revised Guidance includes several important changes to the current Guidance to mitigate risk for controlled SoCs (discussed in more detail below). However, we feel that the Revised Guidance does little to help mitigate risk for uncontrolled SoCs. Worse, if included in the current proposed form, the attempt to achieve the second goal may even be counterproductive to mitigating risk for controlled SoCs. We completely support several of the changes proposed in the draft Revised Guidance for mitigating risk for controlled SoCs. These include: 1) Extending the Guidance to all synthetic oligonucleotides, i.e., both DNA and RNA, whether single- or double-stranded. 2) Extending the Guidance to include manufacturers of equipment that synthesize oligonucleotides, third party vendors, customers, and end users. 3) Lowering the screening threshold to 50 bases and for some oligonucleotides below 50 bases. However, we believe the draft Revised Guidance needs additional work to mitigate risk for controlled SoCs in the following areas: 1) Screening of oligonucleotides shorter than 50 bases. Although we support in principle screening batch orders of synthetic oligonucleotides shorter than 50 bases, we believe that screening oligos as short as the proposed 20 bases will be inefficient. Our experimentation with combinatorial screening suggests a screening performance “elbow” in the range of 30-40 bases: • Below 30 bases, false positives increase notably, which would impose a major burden on oligo providers. • At 40 bases and above, combinatorial screening of oligos is definitely feasible. • In the range of 30-40 bases, screening performance degrades in a manner that is not yet well determined. In addition, we do not understand the 1 micromole threshold for bulk orders. We would like to see either better justification for both of these thresholds, and if lacking, some additional research to set them. 2) Oligonucleotide screening methods. We support using a Best Match approach to help avoid false positives. However, we believe that superior approaches, though not widely available, do exist today and are confident that better approaches can be

developed in the future. Thus, we fully support that the Guidance is flexible and allows 1) other approaches that Providers assess to be equivalent or superior and 2) curated "white lists" of genes that pose no pathogenic risk. We do hope that the Revised Guidance includes ASPR's commitment to either fund research efforts to develop improvements as identified above or to a joint public/private effort (e.g., by NIST), rather than merely encouraging Providers to do so, as suggested in the proposed Guidance. 3) Use of the CCL in defining sequences of concern is currently problematic because the CCL and Australia Group lists are not well maintained. For example, despite the ongoing COVID19 pandemic, no guidance has yet been provided on whether SARS-CoV-2 should be considered as a sequence of concern, and thus it has gone back and forth in CCL select agent status by default based on whether its taxonomic classification is as a sub-taxa or sibling taxa for SARS-1. We thus suggest that if the CCL and Australia Group cannot be more frequently updated, then the Revised Guidance should specifically address exceptions based on emergent information, e.g., in support of rapid response to a public health crisis. With regards to mitigation of risk from uncontrolled SoCs: while we in principle support the notion that some sequences from unregulated biological agents can be "Sequences of Concern", in our view the vague and overly inclusive definition included in the draft Revised Guidance unfortunately offers no practical guidance to providers, manufacturers, and users of synthetic oligonucleotides. One possible outcome is that overly aggressive implementation of the definition will lead to increased false positives, increased screening costs, and even decreased effectiveness. Another possible outcome is that it might even further discourage those providers who do not screen from doing so. If the Revised Guidance intends to recommend screening beyond organisms regulated by the FSAP and CCL we feel it must also include ASPR's commitment to either fund research efforts to develop such an expanded list or to convene a joint public/private effort (again, for example led by NIST), rather than merely encouraging Providers to do so, as suggested in the proposed Guidance. The actual implementation of screening of uncontrolled SoCs must be conditional on the development of an expanded list and/or more detailed guidance on how to develop one. (Other, Academia & Industry).

10. Thank you for the opportunity to provide input on the Screening Framework Guidance. We applaud the government for continuing to review and revise critical biosecurity guidance to ensure that it remains relevant and minimally interferes with the success of the US's burgeoning bioeconomy as biotechnology evolves. The draft guidance

represents some much-needed improvements upon the original, issued in 2010, and we hope you will consider the following additional changes. Specifically, we are cheered by the addition of oligo screening to the guidance. Similarly, we applaud the government for considering risks stemming from outside the genomes of the Select Agents, however, there may be little the government can do at this time that has a significant biosecurity benefit that justifies the cost to industry. We strongly urge the elimination from the guidance of oligos that would be used for PCR only. The timing of the original guidance was based on the recognition that the de novo synthesis of a virus subverted existing government controls on dangerous pathogens themselves by enabling an actor with no access to a pathogen to obtain it via an alternate means. Conversely, PCR amplification technology existed for several decades before the guidance was issued and was not considered to offer a significant dual-use capability that required additional controls. This difference stems largely from the fact that PCR amplification requires one to have a sample of the pathogen, suggesting that controls on stocks still are effective. For this reason, we suggest that the section on “batch orders” and the definition of which nucleic acids are subject to screening be revised to recommend screening oligos only in large enough batches to permit assembly of a large genomic fragment. Given the low margins and demand for rapid delivery of oligos, there is little time for screening of oligos and little funding available to companies to do so without hurting their bottom line. Also, a single, short oligo has little information in it to permit the identification of its dual-use potential. To correct for these issues, we suggest the screening of pools of oligos, each 40 nt in length or greater, that together could produce a 500 bp genomic fragment (a total of 1,000 nt in oligos). The inclusion of pathogens other than the Select Agents in the guidance is a significant expansion. The controls on pathogens themselves other than Select Agents are weak or non-existent, and therefore the inclusion of this concept in the guidance suggests that DNA synthesis companies uniquely take on additional responsibilities for the control of non-listed pathogens. Only if the government were to put stricter controls on the transfer of non-listed pathogens themselves should the additional controls on more exotic routes of pathogen acquisition via synthesis be considered. We applaud the government’s suggestion that sequences of concern beyond those derived from Select Agents be considered. However, currently industry does not know which sequences could be of concern, and therefore the guidance, as it stands, suggests a standard that cannot be met, opening the industry to liability. The government must provide industry with a list or database of sequences of concern in

order to implement this guidance (and the guidance should be changed to suggest that the government realizes this goal cannot be achieved until the database is created). A database of all sequences of concern itself has significant potential for misuse by state or non-state actors, yet it must be shared widely if the guidance is to effectively protect misuse of this segment of the biotech industry with international stakeholders and customers. Also, to be clear, to avoid the need to constantly scrutinize screening thresholds, we suggest that this database be used to identify which segments of DNA, if found to be a “best match” after screening against the entire NCBI (or similarly comprehensive) sequence database, would require follow up screening to ensure that the customer has a legitimate end use. Simply put, this database would add a few sequences to the set of Select Agent genomes that are screened for using a “best match” approach. We also question why the DNA synthesis industry is singled out for providing a route of acquisition for DNA from sources OTHER THAN Select Agents that may have dual-use. If one wanted a dual-use sequence from animals, plants, fungi or microbes (that are not Select Agents), one could simply acquire the source material itself because there are limited controls on the transfer of organisms or genomes off the Select Agent list. We therefore suggest that if the government considers that there are sequences of concern in the genomes of organisms that are not Select Agents, they first consider enacting controls on those organisms themselves and only then add burden on the DNA synthesis industry to prevent acquisition via a more exotic means. Of course, this suggestion implies that dual-use sequences from humans (such as those that encode cytokines and bioregulators) can never be controlled, but the biosecurity benefit of controlling synthesis of this material that can be readily acquired from the malicious actor’s own body is very minimal. If despite the suggestions above, a sequence of concern database should be created, we urge that careful consideration be taken to limit the information risk posed by a database of sequences of concern. We propose that the sequences be limited to those that could make non-Select Agent pathogens as useful in an attack as the Select Agents themselves (by enhancing the pathogenicity or transmissibility of these non-Select Agent pathogens beyond that of any known strain, for example). Information risk is minimized because state actors (who will have access to such a database) already have access to pathogens with as much misuse potential as the Select Agents. Likewise, if all countries know what is in the database, the potential for a state to misuse the information to develop an “unexpected” agent for use in an attack, is also minimized. Conversely, less sophisticated, non-state actors may face

barriers gaining access to the database and exactly these types of actors may need to rely on outsourced DNA synthesis for acquisition of an agent. We suggest that the database of sequences of concern NOT CONTAIN genetic elements that could make a strain MORE USEFUL in an attack than existing Select Agents. The capability to create a strain of a pathogen that is more destructive than any currently known is of significant interest to state adversaries. Since the database of sequences of concern must be shared widely, the creation of a database with these types of sequences will effectively provide this information directly to US adversaries. Moreover, this information is likely to be exploited by only sophisticated actors, who would not need to rely on outsourcing DNA synthesis for the acquisition of a modified agent, and therefore the benefit of this type of sequence of concern is limited as well. We also urge that the guidance clarify that, using a “best-match” approach, hits on housekeeping genes from Select Agents is actually informative, and synthesis companies should carefully consider the risks of supplying DNA for housekeeping genes that happen to match Select Agents better than any other organism to customers without a plausibly legitimate end use. With this clarification, the database of sequences of concern could simply contain sequences derived from non-Select Agents that imbue non-Select Agents with extra destructive power, which is a very small set of sequences. Specific editorial comments: • The definition of “synthetic oligonucleotides subject to screening” is confusing. We suggest simplifying the definition to state 50 nt or longer oligos should be screened if ordered in any concentration and 20nt or longer oligos should be screened only if ordered in quantities of 1 micromolar or more. (We also note our other suggestion obviates this definition by eliminating the need to screen short oligos.) • For oligonucleotides (and other single stranded nucleic acids), length is measured in “nt” not “bp” because they are not paired, per se. We hope that you find this input useful. (Industry)

11. I wanted to follow up with you on some conversations that were had at the recent EBRC workshop on Synthetic Oligo Screening. Some really interesting ideas were tossed around on what issues and gaps are not fully addressed in the draft policy. FFRDCs are uniquely positioned as a neutral party that could potentially help. Two ideas that came out of the meeting that I think an FFRDC could help ASPR with are: 1) Aiding in the development of a Standing Committee. As comments and questions come in about the policy, a Standing Committee could be convened to address those issues. The committee could be comprised of gov’t and industry leaders and could provide further guidance and implementation on specific issues as they arise. 2) An FFRDC could also

help the government develop standards. There was a lot of discussion at the workshop about taking a tiered approach. The level one could be certifying a company could do business in the US. Level two could be that the company is certified to spend government (NIH and NSF) funds. This was discussed as a carrot and stick approach where you have to do the bare minimum, but there is incentive to do more than that. An FFRDC could develop an accreditation process and then also aid in the inspection process to ensure criteria has been met/maintained. Similar to what we do with Biological labs. (NGO)

12. In the decade since issuing the 2010 Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA, advances in synthetic biology introduced new gaps in biosecurity. I commend the Department of Health and Human Services (HHS) for publishing this proposed revision, the Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides. I work at a company that develops a DNA screening platform to identify pathogenic or toxic genes for biosecurity and export control compliance. We create solutions for gene synthesis providers, manufacturers of bench-top DNA synthesizers, and contract development and manufacturing organizations among others. We' support revisions to fill new gaps in biosecurity that stay current with advances in synthetic biology. Based on our experience building screening software, we wanted to offer an overview of our capabilities as they relate to the proposed revisions. Our platform consists of proprietary, curated, and public databases and uses BLAST alongside other tools. The software flags hits to sequences derived from select agents and toxins on Australia Group List of Human and Animal Pathogens and Toxins for Export Control, Australia Group List of Plant Pathogens for Export Control, EU Dual Use Control List, U.S Commerce Control List (CCL), and HHS and USDA Select Agents and Toxins List. Screens are performed by splitting a sequence into windows of 50 base pairs with 10 base pairs of overlap between each window. After aligning each window in the sequence, the software compiles an aggregate report displaying taxonomic identifiers, proteins / genes, functional data, and match statistics. Using identified proteins / genes and functional data where available, the software differentiates between housekeeping genes and genes that contribute to pathogenicity or toxicity. To validate the accuracy of our software, we routinely perform red-teaming protocols with select sequences, testing obfuscation, low similarity select agents, and common false-positives. Based on 100s of screened sequences up to 100,000 base pairs in length, on average, a report is ready in less than 10 minutes. We already support screening single-

or double-stranded DNA as short as 50 base pairs. Ahead of the revisions, we are now building solutions for oligonucleotide synthesizers and third-party vendors. We appreciate the opportunity to comment. (Industry)

13. To whom it may concern, Thank you for the opportunity to respond to the proposed rule. Given our unique experience as one of the most prominent curators and distributors of life sciences materials, we are well-positioned to provide insight into the anticipated impact of the changes proposed in the Federal Register notice. In addition to our unique industry experience, we have actively engaged with the Biosafety in Microbiological and Biomedical Laboratories (BMBL) for many years. We hold many government contracts, each of which provides us a base of experience working with the federal regulatory landscape (e.g., Federal Select Agent Program, Export Administration Regulations) across agencies (e.g., CDC, USDA, Bureau of Industry and Security). Based on our experience, we respectfully ask that you consider the anticipated substantial negative impact on the management and conduct of the following activities covered by the proposed regulations: 1. The requirement to independently identify previously unregulated synthetic oligonucleotides for Sequences of Concern (“SOCs”) that contribute to toxicity or pathogenicity 2. The addition of restrictions for synthetic oligonucleotides that are already controlled under the Federal Select Agents Program and Department of Commerce regulations (CCL) 3. The lack of specific guidance; therefore, the time increases to authenticate end-users as legitimate members of the scientific community and their specific end-use of the SOC; 4. Transfers of SOCs require reporting to the original provider; 5. Notification to customers and end-users when the order contains SOCs; and 6. Unclear who is responsible for tracking these guidelines and how they would be enforced. All six issues create extra levels of complexity, impose an undue burden on our business process, whether sales, service, supply chain, or regulatory, and may not achieve the anticipated policy objectives outlined in the proposed rule. Given this backdrop, we offer the following suggestions to help ensure that companies can comply with any new requirements and that the Government has tailored its regulatory obligations to directly meet its objectives, rather than take a broad-brush approach that may be less than helpful in addressing any Government concerns: 1. The requirement to independently identify previously unregulated synthetic oligonucleotides for Sequences of Concern (“SOCs”) that contribute to toxicity or pathogenicity We agree that there is no curated database of sequences from regulated and unregulated pathogens that pose no biosecurity concerns (i.e., a safelist of genes

that pose no pathogenic risk) presently available. The burden on any company to foresee/predict which sequences from pathogens should or should not cause concern (such as housekeeping genes) becomes unsustainable. We believe that the Agency should develop a database of known SOCs for pathogens, toxins, or otherwise illicit or dangerous substances and make it available for Providers to use to determine if a sequence has the potential to create novel high-risk pathogens. We would prefer that this database be available more readily to those in the industry that require access to work with the information in the database and Providers can contribute to it either before or during a run-in period before the guideline is enforced. Additionally, the restrictions do not define toxicity or pathogenicity, leaving the end user's application of these terms to broad interpretation. For example, antibiotic resistance genes can contribute to pathogenicity, in the presence of antibiotic treatment, but may not be considered as a pathogenic trait upon infection. Therefore, oligonucleotides encoding antibiotic resistance mechanisms may be identified by some users but not others. Toxicity can be assumed to include all genes encoding for toxins made from proteins. Still, basic metabolic by-products can contribute toxicity of an organism (for example, T2 and DAS from Fusarium spp.). Given this understanding, would organizations need to consider any housekeeping gene as contributing to toxicity? Some end-users can also assume contribution to toxicity or pathogenicity requires the entire gene. This leaves open to interpretation how much of a gene needs to be encoded to be recognized as a sequence of concern. There can be significant alignments to genes related to toxicity or pathogenicity without having any impact on toxicity or pathogenicity; for example, an active site for a toxin might be present in the oligonucleotide, but the toxin is useless without a binding site or signal sequence to direct secretion. Likewise, the binding site can be considered as contributing to toxicity by some end users. Without more specific definitions for how much of a gene constitutes identity, these restrictions will result in an inconsistent application of regarding toxicity, pathogenicity, and reporting requirements.”

2. The addition of restrictions for synthetic oligonucleotides that are already controlled under the Federal Select Agents Program and Department of Commerce regulations (CCL) As noted by HHS, some of these products are already controlled under Federal Select Agents Program and/or the Export Administration Regulations. It appears that these controls remain adequate to manage the controls needed for biological and chemical weapons and other dual-use items in the aerospace and defense industry. There are even certain controls under the International Traffic in Arms Regulations

(ITAR) under US Munitions List Category XIV; thus, regulatory oversight and management exists. The addition of further controls, which may or may not be at odds with the requirements of these regulations, seems counter-intuitive and counter to the mission of HHS. As noted below, if HHS wants to add controls to synthetic oligonucleotides that are not already part of the Federal Select Agent Program and/or the export regulations, it appears advisable to work with those agencies to have those SOCs added to the product lists. It is challenging, time-consuming, and costly for businesses to comply with multiple regulations that have different and sometimes competing requirements for the same product designed to have the same end goal (i.e., national security). 3. The lack of specific guidance, and therefore, increased time to authenticate the end-user as a legitimate member of the scientific community and specific end-use of the SOC; The guidance requires the end-use and end-user information to be collected. Still, there is insufficient specificity around the collection, the dissemination, and the ancillary requirements pertaining to that information. This guidance would require distributors to provide specific and detailed end-use information and a comprehensive understanding and ability to evaluate end-use for legitimacy. The guidance lacks specific information on acceptable end-use, the information that would need to be obtained for evaluating end-use, and how the body, whether internal or external, who is responsible for determining legitimacy. The guidance on authentication of end use and end user also lacks the necessary specificity for businesses to comply. We strongly urge that HHS clarify these terms and requires to provide clear and cogent guidelines for industry to operationalize any new obligations. An agency’s failure to provide this level of granularity can contribute to inadvertent noncompliance due to confusion or misunderstanding and can adversely affect both government objectives and industry compliance. Clarification would be particularly relevant in the following areas: what is needed to validate customers, end user organizations, and/or end users. Many organizations maintain programs at the new accounts stage to confirm end-users and collect information regarding the business profile that would affect our products; however, without further guidance, it is unclear whether our business practice would contain the specific information you require. Additionally, the guidance lacks specific ancillary information around the collection of this information. Legitimate questions include: 1) Do we report all this information to HHS? 2) Do we report all of the information back to the original provider? 3) How does HHS confirm that this information is being received and disseminated appropriately (e.g., regular inspections and

certification). 4) What is the recordkeeping requirement for this information when sold through distributors (e.g., is the original seller responsible for getting specific end-user statements from their distributors when the product is sold to the final end-user)? 4. Transfers of SOCs requiring reporting to the original provider (presumably depositor); and The transfer of future sales of SOCs to the original provider raises a range of complex confidentiality, regulatory and privacy concerns, both on the commercial side and government customers. We hold multiple government contracts, which include provisions that limit with whom the information may be shared. As written, the proposed rule does not appear to address this situation as there is no exclusion for the reporting requirement for government contracts. If HHS proposes to implement these additional reporting requirements, coordinating those requirements with other government agency requirements, such as in the government contracts context, will be essential to ensure that noncompliance does not occur under existing regulatory requirements. We may receive SOCs from foreign suppliers, and it is likely unintended by HHS that we would have to supply US Federal Government contract information to a foreign supplier. For commercial sales, challenges exist with providing confidential business information to the original suppliers. We suggest that HHS review this requirement and provide specific guidance on the information requiring sharing versus international privacy laws. Depending on the level of detail needing to be shared, this could be purely confidential business information, or it may run into some issues with General Data Protection Regulation (GDPR) and other privacy information to the extent that end-user information is required to be shared. 5. Notification to customers and end-users when the order contains SOCs. The industry currently uses tools and methods to ensure the legitimacy of Customers, Principal Users, and End Users for trade compliance. This practice may be extended for the purchase or transfer that includes SOC; however, the database referenced above would be critical to the success of screening. Additional due diligence would need to be provided to ensure compliance with guidance and before proceeding with order. 6. Unclear who and how these guidelines would be enforced. The proposed rule lacks granularity and context related to enforcement. How and under what circumstances enforcement will occur provides valuable guidance to industry as it enhances existing compliance programs and ensures that the appropriate risk-based approach is taken. The guidance or insight will allow the regulated industry to know who to contact if issues arise. The frequency of inspections will help us identify the cycle for which we gather information and curate it in a format easily transmissible to an

inspector. Absent even this basic framework raises concerns that companies will follow the requirements differently, if at all, without enforcement. We understand that HHS does not have an enforcement division, and without a permitting requirement, we would request further guidance on how this program will be monitored and enforced. The guidance includes a statement that there will not be a substantial increase in workload to business. We disagree with that assessment. The overall impact of the existing proposal are as follows: 1. The requirements under this guidance are akin to the previous domestic permitting for CDC. The CDC required domestic permits for sales of certain products that required end-user and end-use verification. While the requirements from this proposed guidance remain as onerous on us (i.e., businesses) as that permitting, HHS has removed themselves from this process which alleviates the burden on HHS. Under the CDC permits, we were submitting so many CDC domestic permits that we were asked in an email by the CDC to cease sending more, because we were adding so much time to their workload. This indicates the overall effort required, which now is being born solely by business and will not be increased for HHS. Additionally, this will require us to continually/routinely reclassify all of our products with our product Subject Matter Experts to identify: 1) is it a synthetic oligonucleotide; and 2) is it a SOC. This makes these guidelines potentially even more onerous than the CDC permits. 2. Our customers depend upon us to provide the tools they need for their scientific research in a time-sensitive manner. We estimate that it could affect over 50 products we provide thousands of times per year to customers. These guidelines will require additional customer and product reviews that will impact our turnaround time on orders on critical materials (e.g., monkeypox and SARS-Cov2). In addition, the added resources required to verify both sequences and customer identity may drive up production costs and make the products no longer competitive in the market. Therefore, we may be forced to remove some of the products which are no longer financially viable from our catalog and decrease the access to these necessary products for scientific research. Based on the prior noted impacts, we respectfully suggest either two alternatives: They are as follows: 1. HHS works with USDA, CDC, and the Bureau of Industry and Security to have any SOCs added to the select agent list and/or Commerce Control List. This allows controls to be added to SOCs under existing regulatory regimes for which companies already have compliance programs. 2. If HHS does want to go forward with its requirements, it is suggested that HHS be more detailed in the requirements. Companies require specificity in the requirements to make compliance more effective and efficient. We again thank

you for the opportunity to respond to the proposed rule, and we hope that our insights may assist HHS in the creation and implementation of the proposed rule. (NGO)

14. Thank you for the opportunity to provide comment on the Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides. We appreciate ASPR prioritizing the revision of this critical guidance document. We are an American company enabling the growth of the synthetic biology and genomics markets. We developed a disruptive DNA synthesis platform to industrialize the engineering of biology and our business almost entirely relates to the guidance document. We collaborate with and serve a wide range of industries including healthcare, industrial chemicals, agriculture, defense and academia. We leverage our unique technology to manufacture a broad range of synthetic DNA- and RNA-based products, including synthetic genes and tools for next-generation sequencing (NGS) sample preparation. We are also pursuing longer-term opportunities in DNA data storage and biologics drug discovery, and we actively collaborate with federal government agencies. We commend the U.S. government for its long-term commitment to providing biosecurity-related guidance to the synthetic DNA industry and its customers. The U.S. government was the first government in the world to provide guidance and, twelve years later, remains the only government to fully engage in these important conversations on risk reduction associated with advanced biotechnologies. We believe it's our responsibility as leaders in this space to provide feedback, and see this as an opportunity to establish and foster global norms and best practices. Our core platform is a proprietary technology that pioneers a new method of manufacturing synthetic DNA by "writing" DNA on a silicon chip. As you are aware, synthetic biology holds much promise in healthcare, environmental science, manufacturing, and many other sectors. While we recognize its potential for good, we are aware of dual-use risks and the importance of actively working to ensure this technology is not used for inappropriate purposes. Our company was founded in 2013, three years after the initial publication of the guidance, and we made extensive use of the guidance in our initial biosecurity customer and sequence screening system implementations. We draw on our deep experience as a leading American company in the field and hope that our comments will help inform a robust and thoughtful security framework. We further commend the U.S. government for expanding the scope of the draft revised guidance to cover single-stranded DNA and RNA in addition to the double-stranded DNA already covered under the original 2010 guidance. This expansion reflects leadership in this area and further sets a precedent for future guidance updates

as technology advances. Below, we provide our perspective on key areas of the draft revised guidance based on our business, technology and applications. Expanded Definition of Sequences of Concern The revised guidance: recognizes that screening should evolve to encompass sequences that are recognized to contribute to pathogenicity or toxicity, as information regarding these sequences and their verified function, as well as improved methods to screen become available our company supports shifting the recommendations to focus on sequences of concern (SOC). However, we note this shift risks creating liability for companies by encouraging them to collect and screen against sequences without defining clear criteria for which sequences should be included. We submit that the final guidance should identify such criteria as well as identify who should be responsible for collecting and disseminating these sequences, and what kinds of expertise should be minimally required before allowing a curator to make decisions on whether screening systems will monitor for a SOC or not. Absent governmental guidance on specific inclusion and exclusion criteria, the contents of these databases are likely to vary from company to company, adding yet more variability to a biosecurity context that is already highly variable. In addition, it's not clear what collections could or should be shared internationally to ensure homogeneity in sequence screening (wherever possible) across the global synthesis community. Further, the burden of creating and maintaining a database of this kind is enormous and will be impossible for providers that find implementing even basic screening programs cost prohibitive. To establish consistency among screening programs and ensure that a SOC database effort is appropriately resourced, our company urges the U.S. government to take a leading role in its development and maintenance. We believe it is appropriate for ASPR to work with its partner agencies to explore how this can be best accomplished and to consider public/private partnerships as one avenue to reduce information hazard risks. Reducing screening threshold from 200 nt to 50 nt We support the revised guidance proposal to reduce the screening threshold to sequences of 50 nucleotides for 'best match' to a controlled pathogen, which would trigger follow-up screening. This is a timely and appropriate update in contrast to the original 2010 guidance, which used a 200 nucleotide window size. The reduction in window size to 50 nucleotides is a valuable change as it increases the sensitivity of screening, allowing for the detection of attempts to acquire smaller portions of sequences of concern rather than gene-length sequences. These smaller sequences are typically available for online ordering. To ensure this reduced window size achieves its goal, we recommend pairing

the reduction in screening threshold with a set of recommendations on analyzing the risk posed by the detected shorter sequences. In cases where the short sequences in question represent substantial risk of misuse, we recommend continuing to trigger follow-up screening. These cases would include pools of shorter oligos (so-called ‘batch orders’ in the revised guidance) that could be assembled into longer, functional stretches of a controlled sequence as well as shorter sequences representing short yet biologically functional units (e.g. conotoxins or the SARS-CoV-2 gene ORF10 at only 117 base pairs in length). Including these recommendations for estimating risk is critical; without the inclusion the final guidance would result in frequent alerting and follow-up screening for many low-risk products, some of which may include millions of short DNA sequences. This would raise the cost of screening substantially, hamper businesses’ ability to meet turnaround times for customers, raise the cost of manufacture, and indirectly drive U.S. consumers to ex-U.S. businesses that don’t adhere to these screening guidelines. These disincentives would risk making the follow-up screening process more of a box-checking exercise than an important component of detecting intended misuse. We recommend that, outside of these narrow use cases, alerts on very short sequence regions from non-viral controlled species should be noted (to track and evaluate acquisition efforts over time) but not subject to follow-up screening to allow focus of limited resources on orders with significant potential for misuse. Batch orders We agree with the draft revised guidance that orders for collections of short DNA sequences (often referred to as ‘oligo pools’ in the DNA synthesis industry) may be subject to use for assembly into longer sequences. It is important to ensure these pools are screened to ensure they cannot be used to make longer SOC. While the current draft guidance suggests screening pools in the same way that longer sequences are screened using ‘best match’ homology, we submit that a better and more targeted solution is to screen oligo pools by determining whether they could be used to assemble a longer construct: Are there homologous overlaps between pairs of oligos? Do the oligos strand-swap (i.e. if oligo 1 shares an overlap with oligo 2, and oligo 3 shares an overlap with oligo 2, is the homology with oligo 2 consistent with oligo 2 being the ‘negative’ strand in a final assembly while oligos 1 and 3 would be positive strands?) Are the melting temperatures of the overlap regions consistent across oligo pairs (assembly reactions are most efficient if all of the overlaps used have similar thermodynamic properties)? If the answer is yes to all of these questions, the oligo pool order would trigger additional scrutiny. Further, the draft revised guidance uses a 1 micromole total mass benchmark to trigger screening down to 20bp

instead of 50bp. That is, in our understanding, if a customer ordered a pool of 10 oligos with mass of 0.1 micromole per oligo, the total mass of the pool would be 1 micromole and so would trigger screening down to 20bp instead of 50bp. Assembly techniques, however, do not commonly require that much mass (e.g., our company sells oligo pools in picomolar quantities that are routinely used in assembly reactions) and so the nature of the proposed threshold should be reconsidered. If the goal is to capture pools that are intended for assembly, then the final guidance should recommend that providers screen pools for characteristics compatible with assembly including shared overlaps and overlaps with consistent melting temperatures. Expanding Scope of Responsibility We agree with and commend the U.S. government for recognizing the responsibility borne by the “Institutions, Principal Users, End Users, and Third-Party Vendors of oligonucleotides” and for including the specific recommendations in the revised draft guidance for these entities to ensure they carry out customer screening and/or document the possession and transfer of SOC. These recommendations are welcome and timely, and we suggest taking them further to describe explicitly how the U.S. government believes these parties will be alerted to their new suggested responsibilities. As written, this role would seemingly fall on the synthesis providers to inform the relevant Institutions, Principal Users, End Users and Third-Party Vendors of the guidance and the new relevant recommendations. This risks creating tension between the synthesis provider and these entities, almost all of whom are direct or indirect customers of the synthesis providers. One way to avoid creating this tension is for the U.S. government to create a publicly available website describing these new suggested responsibilities that are available at the publication of the final guidance. The U.S. government could also consider partnering with non-governmental organizations like Federation of American Societies for Experimental Biology (FASEB) to produce educational resources and fact sheets. These resources would allow synthesis providers to refer parties to the new information rather than being responsible for communicating the information. Benchtop Synthesis Device Recommendations We support the recommendations in the revised draft guidance specific to manufacturers of benchtop synthesis devices. To ensure the final guidance is comprehensively effective, we submit that the detailed screening only when customers proactively indicate an intention to synthesize SOC at the time of device purchase does not achieve the U.S. Government’s goal of reducing risk of misuse because customers regularly purchase devices without specific intent to synthesize SOC and later decide to synthesize SOC. Because the revised draft

guidance does not provide any indication to manufacturers of benchtop devices on how to react in such a situation, we recommend against including pre-purchase notification in the final guidance and instead reinforce the importance for benchtop devices to screen sequences in parity with centralized screening providers. By adjusting this guidance, the unintended consequence of a much weaker screening standard for benchtop devices can be avoided. Additionally, we fully support the draft revised guidance section that states these devices themselves must be capable of conducting biosecurity screening and that screening cannot be carried out on the device itself. It is of paramount importance that these devices must be connected to the manufacturer (or a third party) over the internet to conduct biosecurity screening to ensure parity in the quality of screening with that conducted by centralized synthesis providers. We ask that the final guidance specifically highlight the challenge of 'onboard only' biosecurity screening and identify this approach as formally insufficient to determine what sequences may e.g. 'transfer pathogenicity' and in so doing come under FSAP control. Such 'onboard only' screening may work well in simpler contexts (e.g., consumer-grade printers and scanners identifying when a device has been asked to reproduce U.S. currency and refusing to do so) but current biosecurity regulatory controls rely on an understanding of when a sequence 'transfers' pathogenicity - a concept fully local screening cannot understand or reproduce. Follow-up Screening - Suggested Additional Guidance We suggest adding further context and guidance around how providers should think through the specifics around customer screening as well as risk analysis associated with acquisition of specific shorter nucleic acid sequences. For customer screening, the revised draft guidance uses the language in the 2010 guidance and calls on providers to ensure that customers have a 'legitimate, bona fide, and peaceful need' to acquire and use sequences from controlled pathogens. The guidance is silent, however, on what these words might mean and what kinds of intended uses might fall short. The 2010 guidance did include a (very helpful at the time) set of five scenarios but these scenarios did not provide a sufficient level of detail to inform (and help to harmonize) decision-making thresholds across providers. For example, scenario three read: Provider receives a synthetic dsDNA order that incorporates a "sequence of concern;" follow-up screening reveals no legitimate purpose for order or research requirement. The phrase 'legitimate purpose' is footnoted to a quote of U.S. Code Title 18 Section 175(b) but this suggests that any purpose other than weaponization could be considered a 'legitimate purpose.' Customers routinely supply descriptions of their intended uses that are as

minimal as possible - the 2010 guidance even recognizes this by providing sample end-use statements as simple as ‘production of organisms for experimental research studies.’ It would be valuable if the final guidance provided more assistance to providers in attempting to determine whether a user has a legitimate purpose when their description of said purpose can be incredibly simple (and therefore nearly impossible to disprove as legitimate). Specific examples of ‘unresolved concerns’ that the U.S. government believes should trigger contact to the FBI WMD coordinator would be extremely helpful to providers to shape internal policies around this kind of outreach and to harmonize those policies across providers. We further request the final guidance to provide examples of a series of questions that providers could use to carry out more structured conversations with customers. Engaging with customers and questioning the legitimacy of their access can trigger confrontational responses in some customers and the more providers can point to specific questions as recommended by the U.S. government, the higher the chance that providers continue to engage with customers until appropriate answers are provided and confidence is built that use is legitimate. Additional Themes For Consideration While the draft revised guidance addresses several important topics that have changed substantially since 2010, we feel it has left unaddressed several additional topics that remain critical to the uniformity and capability of biosecurity customers, and sequence screening across the country and internationally. The revised guidance does not provide any indication from the perspective of the U.S. government on how synthesis companies should address requests to synthesize DNA that encodes enzymes from pathways that produce controlled substances (e.g. schedule 1 narcotics). We suggest that the U.S. government either affirm that it considers these to be SOC (and that providers should engage in follow-up screening when such sequences are ordered) or affirm that it does not consider these SOC. Unless and until the Government addresses this question, treatment of these sequences across providers will be highly irregular and subject to individual company policy. The revised guidance does not comment on how frequently and at what steps in the manufacturing process customer screening should be conducted. Best practices in export control often suggest carrying out ‘restricted party screening’ during customer onboarding, at the time of order placement and again before orders are shipped. This frequency is designed to ensure that details associated with customers change between the time of initial screening and of final shipment, and this information is taken into consideration when a company makes the decision to ship. We

suggest the guidance echo these best practices as a means of highlighting this best practice from the export control community. The revised guidance does not comment on how to measure the performance of customer or sequence screening and we urge the Government to include at least a brief discussion in the revised guidance on the importance of estimating performance once implemented. Adding suggested metrics to the guidance has enormous potential to help even out the accuracy of these systems across companies in the U.S. and globally. We suggest that the guidance should at least ensure implementers calculate sensitivity and specificity across a wide range of test sequences (ideally with at least one sequence from every organism on the FSAP and Australia Group control lists). This will, at minimum, catch species-specific shortcomings in supporting metadata that may not come to light if testing is limited to a smaller set of sequences covering a more well-annotated set of controlled species. DNA Data Storage Finally, we ask that the Government add a section describing the use of DNA for binary data storage and specifically exclude this use case from the guidance under certain narrow conditions. In this use case, binary data is translated into DNA using a specific encoding strategy (a 'codec') and written as very large oligo pools – a customer has no input into the final sequences that the codec produces. The number of unique oligos required by various encoding strategies to store useful amounts of binary data (1GB - 1TB) will be in excess of 100 million to billions of unique sequences - beyond what most commercially available technologies are capable of today by 1-5 orders of magnitude. The technology to write pools this large has a framework of U.S. government support, standards and scrutiny including the IARPA MIST program, which we are a part of, (https://www.iarpa.gov/research-programs/mist) as well as extraordinary industry investment. It is expected to be commercially available at scale within 2-3 years. To maximize the commercial impact of data storage in DNA, these pools must be manufactured at very low cost but screening oligo pools of this size for biosecurity risks would be computationally expensive using existing technologies for biological applications. We ask that pools created for this abiological use case receive an exclusion explicitly stated in the guidance "if and only if a single company is responsible for both the encoding of the binary data into DNA and the synthesis of the pool of DNA." This removes any risk of including in the pool a minority of oligos that might be used to assemble into a SOC. For providers carrying out only the synthesis of a pool encoded by a customer, the pool should still be subject to the batch order screening guidance since the synthesis company has no assurance that the pool does not contain biologically

relevant sequences that could assemble into a SOC. Without this exemption, this critical and rapidly developing technology will be unduly encumbered as we race to produce a U.S. platform to lead in this area. Summary We urge HHS to finalize the guidance quickly as it will provide significant value to the DNA synthesis providers and community, and will help further harmonize the screening practices across provider companies. It will simultaneously raise awareness among the users of synthetic DNA of their role in ensuring its responsible use, and continue the U.S.'s global leadership in biosecurity and advanced biotechnology. As a leader in this sector, we expect the technology to rapidly advance as it has since the 2010 guidance was written. We see an opportunity to engage across the government and private sector more regularly to discuss the guidance and inevitable updates required over time. We suggest a cadence of an RFI every other year to collect input from the community. Based on the responses to these RFIs, the U.S. government may consider the need for timely updates to certain portions of the guidance. We volunteer to provide support and feedback in any way useful to these efforts as we remain a leader in this sector and a supporter of the U.S. bioeconomy. We thank the U.S. government for its continued interest and attention to this important domain in helping to secure the growing bioeconomy, and we look forward to continued collaboration as technology progress continues. (Industry)

15. 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 orgnization 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 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 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. (NGO)

16. June 28th 2022 To the Office of the Secretary, Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services (HHS): We welcome the call for comments on the Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides issued on 29 April 2022. We look forward to engaging with the Office of the Assistant Secretary for Response and Preparedness in the context of this consultation and in subsequent discussions. We very much hope that the comments that it will provide, which are based on 8 years of research and development of a

revolutionary device, will provide useful feedback to further advance the revised guidance. We were founded in 2014 by three engineers who believe that broadly accessible synthetic DNA is key to improving human health, mitigating climate change, making agriculture more sustainable and solving other challenging problems. We have offices in South San Francisco and Paris, are the first company to commercialize Enzymatic DNA Synthesis (EDS) technology. Our SYNTAX System was launched in June of 2021. We believe that there are many opportunities for the field of EDS and the scope for innovation and job creation are boundless. Our vision is to empower the life science industry and make biology truly programmable by using EDS technology to democratize access to synthetic DNA and accelerate the bio revolution. By enabling broad access to synthetic DNA printing via our SYNTAX Platform, we aspire to drive new discoveries in research, personalized healthcare, therapeutics, diagnostics, and many other vital areas. Biosecurity is at the heart of our business – We are committed to contributing to and developing safeguards that prevent the misuse of this ground-breaking technology without hindering the huge promises for health, environment and research of the growth and innovation in this dynamic field. As we look toward the future, we anticipate that as our technology and capabilities will grow and evolve, we will need to continuously improve our biosecurity controls and safeguards to maintain our leadership position in DNA synthesis technology while supporting the success of our customers. Our comments and recommendations 1. General comments We welcome the opportunity to comment the Revised Guidance and to engage with ASPPR on this crucial guidance that resonates well beyond the U.S. market. We understand that the Publication of the Final Revised Guidance will not establish new regulations. The recommendations are intended to enhance communication between providers and customers to streamline the sequence and customer screening processes, to ensure that all entities are aware of best practices they should adopt to mitigate the risks associated with oligonucleotides encoding sequences of concern, encourage the responsible screening of customers and users, and to encourage the establishment of best practices in the manufacturing of benchtop oligonucleotide synthesis equipment. For the new recommendations to achieve this goal, they would need to provide clear guidance. However, the recommendations in their current form, are too vague to be implemented easily and consistently across the board. We would also caution against creating any market distortion between service and benchtop providers: all actors in this ecosystem must act responsibly and address biosecurity concerns comprehensively.

Given that benchtop devices are providing additional value to the research community, access to the market should not be comparatively more difficult than the situation reserved for service providers relative to their specificities. Arguably, it may be more challenging to garner buy-in from the community or widespread implementation if recommendations set out in the Guidance are unclear, suppress basic research or stifle scientific or commercial innovation. Moreover, the Guidance in its current form shifts a lot of work onto the manufacturer to design the rules to be applied to itself. The revised Guidance also needs to strike a balance between customer satisfaction and adherence to the Guidance, biosecurity and innovation. There is a sense that this balance has not yet been achieved given that the recommendations in the current format shift a lot of responsibility on both manufacturers and customers and remain very onerous. 2. Customer legitimacy: As a leader in our field we are committed to assessing the legitimacy of customers. This information is collected ahead of placing an order and this is systematically documented. This allows us to track all devices that have been ordered and placed with our customers. We have adopted industry best practices to provide access for our customers while deploying solutions to best protect data and confidentiality. As with all our areas of activity we will continue to refine its approach as needs are created and technologies become available. As an International Gene Synthesis Consortium (IGSC) member, we have established relationships with local and national law enforcement and intelligence authorities with whom it can share information to report and to prevent the potential misuse of synthetic genes. It is also actively working with other stakeholders in this ecosystem in order to best understand the challenges and different solutions to address them. Request for clarification and guidance on • Guidelines for collecting & storing customer info: If we are to collect and store customer information, we will need guidance on how that must be done so that we can provide the customer with confidence that we are securing their information properly. • Guidance for cases when devices used outside guidance by legitimate users: Furthermore, guidance needs to be established to protect manufacturers from situations where verified legitimate users use the instrument outside of the recommendations set in user guides and training. Industry and regulatory actors should build guidance on what will constitute reasonable efforts on the part of manufacturers to verify “legitimate uses”. Guidance is also needed on what manufacturers should do if a customer has explicitly disclosed that they are not going to print SOC but in fact do print SOC: what procedures should be used? Who should manufacturers report this to? Will a standardized reporting

procedure or document be established? • Guidance on the notion that “equipment is appropriate for the needs of customers”. How can this be assessed objectively and fairly across the board, and on the basis of what criteria? Is this assessment to be done at outset when device is purchased, through the whole lifespan of the device, upon resale? We have a closed loop system which requires all direct and second-hand customers to order directly from any of our reagents or other supplies. This unique system allows us to control the use of a device and limit use if a customer or user of an instrument is deemed not to comply with the guidance. • Continuous tracking of customers: How can this be done effectively without slowing down the R&D cycle, creating bottlenecks and costs, or heavy administrative burden? What is the purpose of this continuous tracking, and does not the ask go beyond such purpose? • Follow-up screening: Given that a 50bp match (or 20bp for pools > 1um) should trigger follow-up screening, there is a risk of a significant increase in the frequency of follow-up screening. Can the Revised Guidance provide e.g. example scenarios in which a concern was/was not alleviated via follow-up screening, more detail and suggestions around questions to ask when conducting follow-up screening, training materials on how to conduct follow-up screening discussions, as well as situations where pre-screening of customers could allow not verifying the SOCs. • Guidance on how to assess legitimacy: Given the complexity of assessing customer legitimacy, we would welcome having clearer language, best practices, model documents that could support this screening process. In the absence of clear guidance, the different actors in this ecosystem (e.g. industry, scientists) do not have the appropriate tools to be the arbiter of legitimacy. • Guidance on preemptive information provided by customers: Are there other ways in which customers can be helpful to the screening process? If so, can this shared? Our recommendations • The manufacturer should not be responsible for the verification of legitimate use of customers that have been able to demonstrate their bone fide use of the device. We look forward to exploring different options to establish legitimate use. • Benchtop manufacturers can put in place a system to authenticate users that provides robust safeguards, but they ultimately depend on the proper implementation by users (e.g. log in details to be stored and used properly). Best practices, resources and training should be made available to support implementation. • Extending the data logging function to 8 years would not be exceptionally burdensome from a technical perspective, however end-users would need to be informed that information is being collecting and for what purpose. • The revised Guidance should also include measures to incentivize and

support manufacturers e.g. promoting best practices across the industry to encourage take up, or offering resources: training and toolboxes, which will be particularly helpful for companies that may not have the resources to carry out such extensive cross checks. 3. Customer legitimacy and SOCs Request for clarification & guidance • The revised Guidance encourages customers to pre-emptively identify that their orders contain SOC (if known) and provide information that verifies their legitimacy. Will legitimacy documentation be standardized? Vary by SOC level? Can the notion of mechanism for such self-reporting and verification in the ordering process be further refined (what type of document or mechanism is envisaged? When should it be used in the ordering process?) • Given that customers will probably not be familiar with the Guidance and its new recommendations: What tools will be used to disseminate new Guidance in clear and concise language? Customers will need to know when, how and how frequently to update manufacturers on their activities: Will documents be standardized? Different according to the customer or the SOC? • How should providers define SOCs to customers for this pre-emptive step? Our recommendations • A comprehensive approach to biosecurity: In order to address biosecurity risks in a comprehensive way, all actors – from benchtop manufacturers to DNA providers - should ask clients from the outset, when a customer account is set up, whether they will be printing SOC and to update their status immediately should their plans evolve. Such a systematic approach is more likely to address any loopholes that nefarious actors may want to exploit to carry out their actions. The exact information gather should be explored in order to strike a balance between biosecurity screening and customer friendly account creation. • Acknowledging customer responsibility: The specific language in the Guidance is for the manufacturer to install safeguards to ensure legitimate customers can synthesize SOCs. This is expressed in terms of KYC policies and procedures to screen and verify customers have a legitimate purpose for purchasing a device to manufacture oligo sequences. Once a device is placed within the customer's location, the device can certainly impose access controls to specific individuals within the location, but the ultimate responsibility of who is designing and manufacturing oligos at the customer's site rests with the customer and not the manufacturer. • The definition of SOC listed in the Revised Guidance is broad and scientifically ambiguous. Given that this ambiguity will require expertise, time, commitment to resolve, and that the expanded definition will dramatically increase the number of sequences that are flagged for follow-up, the Revised Guidance should include this definition as a best practice rather than a

baseline requirement. • Screening for SOCs: We will use and help to continuously develop the best in market screening technologies by partnering with cutting edge companies and researchers in this field to enable seamless and clear screening at the most relevant level in the order workflow for our customer for SOC. • Raising the floor and the ceiling: The Revised Guidance should take this opportunity to address the challenges of all stakeholders in the ecosystem by encouraging both centralized DNA providers as well as manufacturers and vendors of benchtop synthesis equipment that currently do not screen orders and/or customers to conduct such screening, while also improving screening best practices among responsible providers. 4. Benchtop Manufacturers: secure internet connectivity to screen sequences for SOCs and to authenticate legitimate users Request for clarification and guidance on: • Given the hurdles, challenges and loss of value of connecting devices to the internet for certain customers, namely for concerns around malware and hacking, it would be extremely helpful to have guidance on how the needs of certain bona fide responsible users can be taken into consideration in the development of this Guidance. Clearer recommendations would also be needed for those cases when customers are located in jurisdictions that either bar or severely impinge sharing information through the Internet. Our recommendations • Need to recognize responsible offline use: Given that manufacturers will be advised to screen the legitimacy of customers, and those who want to order SOCs even more stringently, secure internet connectivity appears to be redundant (and may even create other challenges) in the face of customer screening requirements and the layered security architecture put in place by us. • Limits to internet connectivity: An internet-connected device can be partially disabled by the device manufacturer, based on SOCs being requested by a customer who is not authorized to synthesize these sequences. In the case of a remote disability of a benchtop device and the case where the customer is deliberately working around the disabling lock, the liability and the responsibility of the user should be engaged and this behavior should be considered an aggravating factor. • In addition to establishing the legitimacy of customers upon the purchase of benchtop devices, it is imperative that the legitimacy of customers be established and confirmed when reagents and kits are ordered. We are making good use of its closed loop system to maintain oversight of benchtop device use and whereabouts. • The Revised Guidance should also include roles and responsibilities for institutions in the oversight of benchtop device users and in ensuring that each sequence is screened (e.g. in terms of safeguarding access to appropriate and pre-

defined users and ensuring proper log-off, as well as maintain the benchtop devices in secure locations in line with manufacturer recommendations, at all times) and in ensuring that each sequence is screened to ensure that sequences representing potential biorisks are only provided to authorized end users. While we have taken note of the recommendation to operate on a “phone home” model, we are also sensitive to the fact that many of our current users have opted for a “local screening” model. We believe that this model is sustainable and fits well with customers that have • have been prescreened • have demonstrated their bona fide status • demonstrated that they are not based in any barred countries (in accordance with US legislation) Some of our customers have unequivocally expressed reluctance about using the internet at all for a variety of reasons that range from • concerns to secure their sequences in their firewall due to IP and competitive concerns • Concerns related to patient data (in particular for diagnostic activities or personalized drugs) • concerns around their data integrity and protection against Internet threats such as malware, ransomware and other hacking threats (with some companies implementing policies that block internet connectivity) • legal constraints in certain jurisdictions that bar the access to the Internet for certain purposes/users. • Recent past user data exposure by certain service providers after attacks or miss-management. This global and highly competitive market is highly fragmented in terms of internet access and legislation, making it difficult for manufacturers to comply with a blanket recommendation on internet connectivity at all times, or even at all. 5. Sequence screening – technical issues Request for clarification and guidance on: “Non-regulated pathogens and toxins as well as other novel types of sequences or specific types of batch orders, may also pose a risk if they are misused” • This wording is broad and vague, this is especially important given that not everyone working with nucleic acids are microbiologists and may not have the same understanding of what may pose a risk. • Customers are more likely to comply with the Guidance if they fully understand the risks involved with some SOC. Further clarification is needed on how the sequences may be misused and the likelihood of such activities. “Individuals with no legitimate, bona fide, and peaceful need should be prevented from accessing genetic materials that could contribute to pathogenicity or harm, even when they are not from FSAP or CCL listed pathogens or toxins” • Who decides who has a legitimate need to access genetic materials? • Who controls the technology, and ultimately the research itself? • Without further clarification, the premise of enforcement will be challenging to implement. • Definition of toxic or pathogenic sequences if they are

not part of FSAP or CCL “Purchasing or synthesizing oligos could enable individuals without a legitimate and peaceful purpose to possess genetic sequences that would create risk if misused” • Clarification is needed on who determines intent. Who determines if something is (or could be) misused? • Is consideration for misuse at the ordering stage, during the experiment or after the experiment is conducted? Each stage would require different people to be involved and aware of the risks and understand what to do about them • Clarification on how to deal with current existing fleet of unregulated/recorded phosphoramide oligo synthesizer and free-access to phosphoramidite reagents Revised guidance…recognizes that screening should evolve to encompass sequences that are recognized to contribute to pathogenicity or toxicity, as information regarding these sequences and their verified function, as well as improved methods to screen become available (or as feasible) • Who will decide what is added to the list? When will something come off the list? What process will be put in place to ensure that any decision has a sound scientific basis? • How will the guidance be communicated to the research and safety communities? To the public? • Who will train the staff to manage screening? Who will enforce it? Synthetic oligonucleotides subject to screening: 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 20 bp or longer if ordered in quantities of one micromole or greater • Screening sequences at 50bp can determine if they are a match to a potential sequence of concern or are a best match to a regulated pathogen or toxin sequence, will significantly increase the number of oligonucleotides that are subject to screening and will expand the pool of actors expected to adhere to the guidance. What additional resources, tools, and incentives to support adherence will be developed to help absorb the economically challenging impact of screening? • Given that screening sequences of 50bp, can be potentially technically challenging, any recommendations on such requirements should be further discussed and refined with screening providers to ensure that they are feasible and accurately captured before being added to the revised Guidance. Expanded scope to include batch orders of oligonucleotides. • Given that the technical tools for screening batch orders of oligonucleotides are not fully developed, and that the most effective methods are not yet clear, can ASPR support the development of effective screening strategies and best practices? 6. Periodic review, evaluation, and improvement of the Guidance We applaud ASPR for adding this section of review, evaluation and improvement of the Guidance; thereby opening an important, valuable discussion on the challenging topics set out in

the document. As we continue to grow and scale up its activities, we will continue to seek opportunities to coordinate and harmonize our approach with this new Guidance. We strongly recommend: • Setting up a revision and evaluation channels to solicit feedback e.g. every two years • Given that biotechnology is moving fast, we also recommend allowing the private sector or the research community to share information about new developments on an ongoing basis, namely via a stakeholder group We also believe that this section will greatly contribute to implementing the revised Guidance in a light touch and efficient manner, that will support a transparent, competitive and innovative market. Thank you again for the opportunity to share our perspectives. It is our hope that we can serve as a partner to ASPR to help ensure broad compliance with this revised Guidance. (Industry)

17. The HHS Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA aims 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. By demonstrating that certain biological agents can kill more people than any nuclear weapon, the COVID-19 pandemic has underscored the importance of limiting access to nucleic acids that can be used to assemble harmful agents capable of autonomous spread. Thousands of individuals worldwide currently possess the technical skills to assemble many different families of viral agents from synthetic DNA using published reverse genetics protocols. This number will only grow with time. As virology and biotechnology advance, new agents and sequences of concern will be identified. For example, numerous actors have announced their intent to credibly identify viruses capable of causing new pandemics and publicly share their genome sequences. If successful, any of thousands of individuals will be able to cause new pandemics – but only if they can obtain synthetic DNA corresponding to the newly identified genomic sequence of concern. We applaud HHS and ASPR for recognizing the importance of assisting providers in screening DNA synthesis orders to limit the proliferation of access to emerging hazards capable of killing millions, and suggest the following additions and clarifications to the revised guidance by type of screening: Customer screening is used to ‘establish the legitimacy of customers ordering synthetic dsDNA sequences’ Providers are expected to verify customer identity by asking for names, addresses, and any affiliation for comparison to proscribed lists. Customers lacking an affiliation should be subjected to follow-up screening. However, there is no

mechanism to link customer information to a single enduring identity, nor any way to ensure that the customer is the person they claim to be. We recommend that: *Customers share their ORCID when placing a synthesis order* - ORCID is becoming the standard for identifying researchers in the life sciences, and consequently can serve as a common means of uniquely identifying customers - Customers who lack an ORCID should be encouraged or required to obtain one - Providers may wish to allow ORCID-based login to their ordering portals - Identity theft is a plausible way to evade screening in order to obtain sequences of concern - Customers can initially be required to use two-factor authentication with an authorization app *Providers encourage customers to use hardware keys for two-factor identity authentication* - ORCID should implement hardware-based authentication, which providers can require for ORCID-based login and ordering *Benchtop devices require hardware-based user authentication to enable customer screening before use* - A benchtop device user who is not authenticated is a customer who cannot be screened Sequence screening is used ‘to identify when “sequences of concern” are ordered’ Providers are encouraged to screen for sequences matching agents on the Select Agent List, and are required to screen exported orders for sequences matching CCL-listed agents or toxins. As SARS-1/SARS-2 hybrids were recently added to the Select Agent List, and the frequency of such additions is expected to rise, providers must regularly check for updates. The U.S. government recognizes that many sequences not on either list can be used to cause harm, and encourages providers to develop best practices for detecting such sequences, but does not consider the generation of a comprehensive list by the government to be feasible. We agree that there are disadvantages to a government-provided list, but believe that the pandemic has highlighted the particular hazards of potential pandemic pathogens, virtually all of which are included within the set of mammalian and bird viruses. More generally, a collectively-maintained and centralized list of sequences of concern would have many noteworthy security advantages. Most importantly, benchtop devices must have a secure internet connection to screen for pandemic agents that will be identified in future, and cannot store the screening criteria on the device for security reasons. Benchtop device screening must additionally guard against permutation attacks enabled by the customer having access to the synthesis device. We recommend that: *Providers update their list of sequences of concern daily by monitoring changes to the Select Agent and CCL Lists as well as the primary literature* - The recent addition of SARS-1/SARS-2 hybrids to the Select Agent List underscores the changing nature of the threat landscape

- As some DNA synthesis services offer next-day shipping, providers using their own database should update it at least daily to include newly identified sequences of concern *Providers consider all mammalian and bird viruses to be sequences of concern* - Pandemic-capable viruses can demonstrably inflict a thousand times as many casualties as anthrax or any other agent incapable of autonomously spreading around the world - Mammalian and bird viruses are potentially pandemic-capable - Working with more than 2/3 of the genome of a eukaryotic virus already requires institutional biosafety approval per Section III-D-3 of the NIH Guidelines - There is no justification for performing virological experiments without evidence of adequate organizational safety and security precautions, so follow-up screening is always warranted *Providers adopt a centralized, collectively maintained database of sequences of concern* - Any database maintained by the U.S. government will be less comprehensive and up-to-date than a database that is collectively maintained - A collectively maintained database would benefit national security because agents listed as hazardous by the U.S. government could be used by rogue states or extremists to credibly threaten the United States, whereas threats to use agents listed in a non-governmental database against the United States will be less politically credible - Sequences should only be added to a public database if their misuse potential has already been publicly described, because their inclusion would render them more attractive targets for terrorists intent on causing harm - Systems capable of screening for emerging non-public sequences of concern without disclosing the identity of the sequences in question would benefit security while avoiding the disclosure of information hazards, and consequently should be encouraged for national and international use *Benchtop synthesis devices must, without exception, require a secure Internet connection for operation* - Any benchtop synthesis device that cannot be rapidly updated will allow skilled individuals to produce any and all pandemic-capable agents that are publicly identified in the future - By analogy to the closest equivalent in lethal potential, a benchtop capable of producing novel pandemic-capable agents is equivalent to a machine that can build nuclear devices on demand - If the benchtop synthesis device can operate autonomously without a secure Internet connection, a motivated user could refuse to connect it to the Internet, thus preventing updates *Benchtop synthesis devices never maintain screening criteria on the device itself* - Storing screening criteria on the device likely permits extraction and publication of the criteria, thereby providing everyone in the world with unlimited attempts to design orders that will evade screening while still yielding a functional agent - Protecting information on any device under a

motivated user’s direct physical control has proven to be extremely difficult *Screening methods for benchtop devices guard against attacks that permute the bases in a DNA sequence order and change the reagents in the device accordingly* - For example, swapping every “A” for a “T” in the order and swapping the reagents that determine whether an “A” or a “T” is added would allow a user to generate a desired sequence while sending the permuted sequence for screening *Providers and device manufacturers be encouraged to use cryptographic methods of screening without disclosing the contents of the order to accommodate customers concerned with protecting trade secrets, which may be especially common among users of benchtop devices* Follow-up screening is used 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’ Because many domestic customers are already subject to the NIH Guidelines and must obtain institutional biosafety committee (IBC) approval of many experiments, providers can communicate directly with IBCs during follow-up screening. We recommend that: *Providers work with institutional biosafety committees to ensure that customers have permission to access sequences of concern* - All organizations receiving federal funding from an agency requiring compliance with the NIH Guidelines are already required to have an IBC-approved biological research registration describing the genes that they are permitted to work with - All sequences of concern that originate in organisms listed as BL2 or higher already require IBC approval before experiments can be initiated - Any experiment involving more than two-thirds of the genome of any eukaryotic virus already requires IBC approval before initiation - For customers with an IBC, providers can decline to fulfill orders corresponding to large segments of mammalian or bird viruses until provided evidence of IBC approval - For customers without an IBC, providers can fulfill orders corresponding to large segments of mammalian or bird viruses as they believe justified, but should notify the FBI of the transaction We thank HHS and ASPR for taking these important issues into consideration. (Academia)

18. We are an industry-led group of gene synthesis companies and organizations formed to design and apply a common protocol to screen both the sequences of synthetic gene orders and the customers who place them. In collaboration with national and international government organizations and other interested parties, we also promote the beneficial and responsible application of gene synthesis technology while safeguarding

biosecurity. Further, we screen and vet policies implemented by our members to ensure compliance with national and international standards for biosecurity. We commend the Assistant Secretary for Preparedness and Response (ASPR) and the inter-agency working group for its leadership in developing and issuing screening standards along with the government's continued engagement in the conversation on risk reduction practices associated with advanced biotechnologies. It is our mission to continuously improve best practices and, as such, we support the government's efforts to issue revised guidance on the subject of biosecurity screening. We offer these considerations as a group of organizations with the interest of ensuring compliance with standards including those issued by the government. Sequences of Concern As a baseline, Our companies screen against all pathogen and toxin genes as specified in the US Select Agents and Toxins List, the Australia Group Common Controls List, and the EU Dual-Use List. We recognize that this approach is limited as these lists are not complete in the sense that there are other sequence components that, alone or in combination, can be misused to cause harm. These lists also are focused on the level of the organism, which is inefficient for screening purposes as most sequences in an organism's genome do not 'endow or enhance' pathogenicity. For these reasons, we support the government's proposal to shift to screening for sequences of concern. It is our view that this would further emphasize that the focus should be placed on the broader goal of preventing the use of synthetic genetic material for nefarious purposes. However, we would like to offer our perspective based on our work to assemble and continuously curate a 'restricted pathogen database' to include data from all organisms on the Select Agent list, the Australia Group Common Control List, and other national lists of regulated pathogens. We task ourselves with updating this list to include all gene sequences identified as potentially hazardous by authoritative groups such as the US Centers for Disease Control and Prevention, the Australia Group, and the US and European governments, and we can report that this effort is laborious and resource-intensive. We understand that any list could quickly become outdated, and as such, we are deeply committed to the long-term success of this project. While shifting to a sequence of concern basis could, in principle, dramatically improve current screening practices, we are concerned that many entities lack the resources to catalog such sequences on their own as individual actors – already many in the broader gene synthesis community are unable to meet the current standards that have been put into place by our members. Even if an entity is willing to put forth the resources to develop its own database, and to maintain

that database over time, the proposed guidance does not detail how entities wanting to comply with these standards may do so. Thus, we are also concerned that the draft revised guidance may shift liability to industry and inadvertently lead to more variability in screening programs across the world. At a minimum, the government should provide specific details on how each entity subject to the guidance would identify a sequence of concern. Moreover, we urge the US Government to engage with international efforts to establish harmonized screening approaches. In particular, it would be important for the US to invest in and support the development and maintenance of a sequence of concern database (perhaps via public/private partnership) so that industry can implement consistent, high-quality sequence screening approaches, flagging sequences that are verified to be of concern by the US Government, without significant additional burden on each individual entity in the gene synthesis community. Lastly, we note that the revised guidance contains language recommending the use of predictive algorithms when sequences have little or no homology to naturally-occurring sequences. We would like to take this opportunity to state our support for the development of risk assessment software that can be broadly used by the gene synthesis community. Synthesis providers, however, are not well-positioned to develop such algorithms given the required fundamental knowledge around protein structure and function relationships and the complex nature of the machine learning-based approaches required to estimate what kinds of sequence would preserve or create a biological function that might be subject to misuse. Once again, we believe it would be impactful for the US Government to make investments in this space. Screening threshold we are generally supportive of the proposal to reduce screening threshold sequences for ‘best match’ to a controlled pathogen triggering follow-up screening. In the final guidance, we recommend pairing any new threshold with a set of recommendations for analyzing the risk posed by a detected shorter sequence. That is, when is sufficient risk posed by acquisition of 50 base pairs of a SOC? Without a framework for estimating risk, the final guidance is likely to result in very frequent flags for 50-120 base pair sequences from controlled organisms or toxins that do not themselves pose any direct risk of misuse, such as oligos used for target enrichment in sequencing or as primers for pathogen detection. We are concerned that this approach dilutes the follow-up screening process and creates burdens for an already labor-intensive process. Instead, the government should additionally recommend that in cases where the short sequences in question represent, on their own, a substantial risk of misuse (e.g. a very short ORF from a controlled virus,

a conotoxin, or a functional component of a longer SOC), this should continue to trigger follow-up screening. Based on the pragmatic experiences of our members with order screening “in the field”, we propose the following guidance for determining when a potential sequence of concern should be considered to have significant potential for misuse, and thus require follow-up screening: 1. If the sequence is from a gene for which it is known which domains are functional with respect to the toxic or pathogenic activity of concern, then it is specifically those domains that are considered to be of concern. 2. If the sequence is from a gene that is known to have toxic or pathogenic activity of concern, but its specific functional domain architecture is not known, then all of the gene is considered to be of concern for genes less than 360 bp / 120 aa, or all except for the first 120bp / 40aa, and the last 120bp / 40aa for genes larger than 360 bp / 120 aa. This compromises between the need to avoid impeding legitimate oligo applications that are not of concern (e.g., sequencing and detection), while still controlling enough of the gene to prevent screening evasion via oligo pool assembly. 3. If the sequence is from a listed bacterial or eukaryotic organism and is not from a region known to have toxic or pathogenic activity of concern, then the sequence is not of concern. This recognizes that 1) in bacteria and eukaryotes, most of the genome has little relationship with the properties that make an organism a threat, and 2) poorly understood materials have little potential for misuse, even if at some time in the future they may be discovered to have a link with pathogenicity. 4. If the sequence is from a viral or viroid threat and is from a region whose functional relationship to toxic or pathogenic activity is not well known, then it is still considered to be of concern. This recognizes that the genomic content of these classes of threats is typically tightly selected, and thus should be assumed to be of concern unless specifically known otherwise. This framework covers the case of pools of shorter oligos that could be assembled into longer, functional stretches of controlled sequence as well as shorter sequences representing short yet biologically functional units. Outside of these narrow use cases, however, alerts on very short sequence regions would be noted but not be subject to follow-up screening, in order to prioritize the use of follow-up screening resources on those orders with the highest risk of misuse. We thus request that the government either 1) adopt this framework for determining level of concern, 2) collaborate with us to determine a framework, or 3) provide a framework of its own devising that addresses all of the concerns enunciated here. Further, the draft revised guidance uses a 1 micromole total mass benchmark to trigger screening down to 20bp instead of 50bp. Assembly techniques, however, do not commonly require that

much mass and as such the specified thresholds established by the guidance should be reconsidered. If the goal is to capture pools that are intended for assembly, then the final guidance should ignore mass and recommend that providers screen pools to find groups of oligos that have characteristics compatible with assembly (e.g., shared overlaps and overlaps with consistent melting temperatures). Expanded scope of the responsible parties We are generally supportive of the government issuing recommendations to an expanded scope of responsible parties. We agree that many actors in the gene synthesis community, including providers, tool manufacturers, third-party vendors acting as distributors, principal users, and end-users, have a role to play to ensure that these technologies are not misused. However, this is a significant shift in current standard practice, so we recommend that the government take a lead role in educational efforts by releasing additional resources and partnering with academia, coalitions, and trade organizations to help support entities seeking to comply with the updated recommendations. This will ensure that the burden of education and compliance is not predominantly placed on providers that already comply with ASPR guidance. Record keeping We require that members retain records of every gene synthesized and delivered for a minimum of 8 years after shipping, including at least the following: (a) the synthetic DNA sequence; (b) the vector (if applicable); and (c) the recipient's identity and shipping address. Further, we require that members retain records of every gene sequence screening result for at least 8 years. We greatly appreciate that the revised guidance aligns with these recommendations. Pre-screening recommendations To ensure the draft guidance is comprehensively effective, we submit that pre-screening only when customers proactively indicate an intention to synthesize SOC at the time of device purchase does not achieve the government's goal as customers regularly purchase devices without specific intent to synthesize SOCs and later decide to synthesize SOCs. However, we believe that customer screening should identify categories of customers (e.g., bona fide with established affiliations) that are pre-authorized to print specific categories of SOCs (since different categories SOCs involve different concerns, it will generally not be appropriate to pre-authorize the full range of SOCs). We therefore believe that all actors - benchtop manufacturers and providers - should ask clients from the outset, when a customer account is set up, whether they will be synthesizing SOC and to update their status immediately should their plans evolve. Benchtop synthesis device recommendations We support the recommendations in the revised draft guidance including those directed at manufacturers of benchtop synthesis

devices. Additionally, we fully support the draft revised guidance section that states these devices themselves must be capable of conducting biosecurity screening and that, except for specific customers that have successfully passed more stringent customer screening with respect to specific categories of SOCs, screening should ideally be carried out through the device itself. We look forward to working with the government to explore what best practices for these more stringent customer screening requirements may entail. Absent stringent, SOC-specific customer screening, we agree that these devices should be connected to the manufacturer (or a third party) over the internet to conduct biosecurity screening to ensure parity in the quality of screening with that conducted by centralized synthesis providers. We further suggest that it is desirable that benchtop devices should screen at all relevant accessible and clear levels (where more context is available) of sequence information, e.g., if a device is given a gene target for assembly or a genome edit plan that is then broken down into oligos to implement the plan, the benchtop device should screen at the higher level, as well as at the level of the actual oligos to be synthesized. Screening systems Lastly, we encourage the updated guidance to address the challenge of estimating the performance of sequence screening systems. These systems are implemented by individual companies but all have a common goal – to identify orders for controlled sequence and ensure proper follow up and licensing. We recommend the guidance suggest periodic 'red teaming' (that is, allowing expert third parties to attempt to order controlled sequences without a screening system alerting) and outline specific metrics that providers should collect during these exercises so that screening systems and performance expectations can be compared across provider implementations. If the government were to include this information in the next iteration of the Guidance, it would ensure that all domestic manufacturers are adhering to the same standards, improve the uniformity of screening across the industry and allow those screening practices to keep pace with future advances in technology. Given that both HHS and the Department of Commerce oversee aspects of biosecurity for synthetic DNA, we ask that the two agencies also work to ensure that export licensing requirements align with the new screening recommendations within the revised guidance. Periodic review, evaluation, and improvement of the Guidance Given the fast pace of advancement in nucleic acid synthesis, we would like to encourage the government to solicit feedback from the synthetic oligonucleotide community at a regular interval, perhaps every two years via request for information (RFI). We and our member companies would be natural partners in this process, supplying responses for evaluation

by the government. After considering the responses to each RFI, the government may identify portions of the guidance that need updating and we would encourage this lighter weight, more frequent pace of updates so that the guidance keeps pace with changes in industry and technology. Thank you again for the opportunity to share our perspectives. It is our hope that we can serve as a partner to the government to help ensure broad compliance with this updated guidance. (Industry)

19. Introduction The issuance of proposed Revised Guidance for the DNA synthesis industry is laudable and of utmost importance to a safe, secure, and productive biological research ecosystem capable of addressing the great societal challenges of this time. We hosted an NSF-supported workshop with key stakeholders across the industry as a forum for discussion and debate around elements of a robust Guidance framework. This “Part 1” submission responds to two elements of oligo screening that are central to the proposed Revised Guidance and that were considered at length during our workshop: 1) customer screening and responsibilities; and 2) sequence screening: sequences of concern. A “Part 2” submission will address 3) sequence screening: technical considerations; 4) the sequence screening ecosystem; 5) benchtop synthesis equipment; and 6) emerging technologies. Risk cannot be eliminated from biological research and development, so we appreciate the care with which USG is working to balance the very real imperative to fervently support research with the implementation of security measures that are appropriate for the hazard space. We hope that our comment will be useful in the development of final Revised Guidance. 1: Customer Screening & Responsibilities The proposed Revised Guidance has an expanded scope that includes guidance for Customer, User, and Third-Party Vendor best practices, which would necessitate stakeholder education to enable and encourage compliance. Asking these stakeholders to invest their attention in security is certainly a worthy and positive endeavor and workshop attendees broadly support. However, there was not unanimous agreement on how or by whom this education could be facilitated, the degree to which it might alleviate the burden on providers of synthetic DNA, and the security benefits. 1.1 Verifying customer identity and legitimacy our workshop participants highlighted areas where greater specificity in the Guidance could help providers determine customer legitimacy (which would also help customers submitting legitimacy documentation), as well as new approaches to determining customer legitimacy. 1.1.1 Clarification and specificity: -The given definition for “Verifying Legitimacy” says that the recipient of materials should be a “legitimate member of the scientific community.” Who does USG

deem to be a “legitimate member of the scientific community?” Examples where “legitimacy” might be unclear include: members of the DIY bio community; a customer who has not published research or presented at a conference in ten years, but now claims to work for a new biotechnology company somewhere in the world; a customer whose business address has the appearance of an apartment building. -What does it mean for a Customer or Principal User to verify the legitimacy of an End User receiving a SOC? This has the potential to give license to someone in a position of power to ask a trainee personal questions. If an undergraduate has some past legal issues, are they disqualified from working with any SOC? Does a PI have a right to know that background and make decisions about a student’s legitimacy? The Guidance could instead ask Principal Users or Customers to make sure that the End User has the requisite training and/or facilities to handle a SOC. -Increase specificity and clarity on what documentation demonstrates legitimacy. Expanding on the examples already provided in the proposed Revised Guidance, a final version could include specificity such as: -A customer ordering a sequence that is on the CCL or Select Agent or Toxin list can demonstrate legitimacy through i) proof of registration or licensing with FSAP or DOC AND ii) documentation of an institutional biosafety officer. -A customer ordering an unregulated SOC can demonstrate legitimacy through i) documentation of an institutional biosecurity officer AND ii) providing relevant publication history OR supporting business license OR proof that a federal agency is funding the customer to work with SOC(s) in question OR sharing a description of intended use signed by an institutional biosecurity officer. Increased specificity would help DNA synthesis providers comply with Guidance, help customers submit appropriate documentation, support continuity across industry, and lend “top cover” to providers, whose customer interactions benefit when providers can support and explain their documentation requests with explicit passages from Guidance. A great challenge is providing the specificity and clarity needed to be useful to industry while maintaining flexibility for unique circumstances, such as customers changing their research focus in response to the emergence of a novel pathogen. 1.1.2 New approaches to customer legitimacy that could be enabled or endorsed by USG: -Customer seal of legitimacy or “allow lists:” Some EBRC workshop participants favored increasing the relative focus on customer screening as compared to sequence screening, noting that sequences themselves are almost always benign; it’s how a customer uses them that matters. Known or verified customers could be placed on allowlists or given a seal of legitimacy for given types of

sequences for some amount of time, after which the customer would have to be re-verified. All sequences would still be screened, but follow-up would not be necessary for customers ordering SOCs for which they have approved uses. Implementation would be challenging, particularly on an international scale. -Designating access tiers: Potential supporting documentation for legitimacy tiers are described above for customers ordering SOCs, while a customer who has been verified (has an address, has a payment mechanism) could order any sequence that is not a SOC. 1.2 Customer submission of legitimacy documentation during ordering In suggesting that customers provide information to verify their own legitimacy when ordering SOCs, the proposed Revised Guidance has the potential to streamline customer screening and ease provider burden. This is a laudable goal, although would face some significant challenges: -Companies would each need to build and integrate into their ordering platforms a mechanism for customers to easily submit this information as well as infrastructure to secure, track, and structure the information in a way that is useful to providers and eases customer and follow-up screening. -Without substantial efforts to educate customers on why, how, and what documentation they should submit, companies might invest in such a mechanism only to have it go unused by customers. Putting the responsibility for education solely onto providers would nullify the intended provider benefits (efficiency, burden alleviation). Therefore, a concerted effort to educate customers may need to come from funders, institutions, or others. Otherwise, this practice is unlikely to achieve its goals -Providers may find it challenging to interpret documentation submitted by customers. -Providers have found that customers vary in how forthcoming they are with information to verify legitimacy, so providers might still need to do significant follow-up. -Without a public, common definition of a SOC, customers will be unable to determine if they are ordering a SOC that requires verification of legitimacy. Customer education regarding SOCs (definitions, identifying, etc) would be needed. Customer submission of legitimacy should only be incorporated into final Revised Guidance if industry supports it, if a plan for customer education is developed, and if greater specificity can be provided. 1.3 Third-Party Vendors The inclusion of third-party vendors in the proposed Revised Guidance provides an important additional layer of security that alleviates a burden on providers of synthetic DNA. Previously, providers did not have a clear understanding of if/how to conduct customer screening or follow-up screening for SOCs ordered by third-party vendors. Encouraging third-party vendors to assume that responsibility was generally viewed by attendees as appropriate. While there may be a burden for some to

develop necessary systems, it is important that they do. Some additional clarity as to the definition of a third-party vendor would be useful. Workshop attendees were not in complete agreement about what “reformulation” of oligos encompasses, e.g. is all assembly and cloning included in “reformulation?” Specific vendor types that may or may not be third-party vendors depending on this definition include those that order a coding gene sequence and express it to make proteins, those that order oligos and assemble them into a gene, those that order DNA and package it into a virus, and those that order a gene sequences and clone it into a vector. The definition of Third-Party Vendor might also be expanded slightly to include organizations that distribute synthetic oligonucleotide constructs. For example, plasmid repositories do not “order oligonucleotides from Providers,” but do have an important role to play in the security landscape and the Guidance would be strengthened by their inclusion. It might also be useful to explicitly state that a Customer of a provider might be a third-party vendor, increasing clarity that a provider must notify a third-party vendor when screening identifies a SOC, and third-party vendors would be responsible for notifying the originating customer. If “reformulation” includes the incorporation of synthetic DNA from providers into constructs, it might be appropriate for third-party vendors to conduct sequence screening themselves and incorporate the context of the entire construct, when applicable; however, capabilities for assessing genomic context are still developing and require dedicated attention and resources. 1.4 Tracking SOCs The proposed Revised Guidance “recommends recording transfers of oligonucleotides containing SOCs from Principal Users and End Users to any other individuals not listed in the original order, such as through a Material Transfer Agreement (MTA) or another sample tracking process.” While this is a laudable goal and there would be a benefit to tracking at this level, there would be challenges to implementation in academic settings. Academic institutions generally lack the tools, infrastructure, and staffing for universally maintaining consistent records for chemical and biological inventory management. Thus, in these resource-limited settings, tracking of SOCs might not become a priority beyond practices currently in place for MTAs. It may be more feasible in academic settings for individual labs to track the SOCs they order. The consistent turnover and changing responsibilities within labs, especially those with small budgets that do not have an administrative support person, would challenge the consistent implementation of tracking SOCs, so education efforts would have to be consistent and robust to support such ongoing tracking. Above all, the tracking of SOC transfer from Principal Users and End

Users to other individuals would require Principal and End Users to understand which sequences constitute SOCs. A User might know their sequence is of concern if a DNA synthesis provider notifies them as such during the ordering process, as encouraged by the proposed Revised Guidance. However, without a consistently implemented definition of SOC, providers will likely have different interpretations and screening databases, and thus SOCs will be defined and tracked inconsistently. Additionally, the number of sequences currently housed in laboratories across the country (and world) that "contribute to toxicity or pathogenicity" is gargantuan, and they are inconsistently annotated. Developing tracking systems and incorporating such sequences into them is a very significant challenge and benefits may not outweigh the costs. With these considerations in mind, recommending the tracking of SOCs might not represent the most effective approach to enhancing security concerns posed by SOCs, especially since regulated sequences are already subject to transfer regulations. 2: Sequence Screening: Sequences of Concern 2.1 Defining SOCs Providing a description of what constitutes a SOC is perhaps the greatest challenge of developing meaningful Guidance. It is appropriate that USG encourages providers to screen for sequences beyond those from FSA and CCL lists, but the Guidance would greatly benefit from further clarity and specificity. EBRC Workshop participants discussed the benefits of defining a robust and attainable "floor" for screening while providing guidance to institutions working to raise the "ceiling." -A framework constituting the floor (minimal screening attainable or even expected by all) could be drawn from the 2010 Guidance: "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." Setting an attainable floor is important because some effort to screen by a provider is better than no effort, and minimal efforts can be built up over time. -A clear framework is needed to determine which sequences might be included under a ceiling (best, industry-leading screening approaches) regime. USG could develop such a framework for determining if a given sequence is a SOC and socialize that throughout the synthetic oligonucleotide industry, specifically, and the emerging biotechnology industry more generally. In doing so, USG might consider that: -A vast number of sequences can "contribute to toxicity or pathogenicity" threatening to "Public health, agriculture, plants, animals, or the environment." For example, all antibiotic resistance sequences, which are used in most

aspects of molecular biology, would be of concern under this definition. So would Bt genes, which are expressed in millions of acres of corn and cotton and are highly toxic to specific insects. Thus, to avoid the dilution of follow-up screening efforts by excessive flags for SOCs, it may be appropriate to narrow the given definition of SOC, or provide additional guidance for which SOCs necessitate follow-up screening. -To help bound which sequences are of concern, one workshop participant described using functions to define SOCs, e.g., sequences that cause direct damage to a host, that subvert host immune responses, or that enable host invasion, dissemination or adherence (http://doi.org/10.1128/iai.00334-21). The same participant suggested that, for greater specificity, USG could 1) determine host taxa that are most valued/cared about/necessary to protect; 2) identify the pathogens most concerning for those taxa; 3) document the sequences that enable pathogenesis for the identified pathogens. This approach, or more broadly listing priority functions of concern, would enable those pushing the ceiling higher to focus their efforts on the highest impact sequences. Annotating and curating sequences based on those functions would be arduous, but previous efforts demonstrate that with investment, this can be done. -The Guidance should recognize that many sequences that are not directly pathogenic or toxic can be used to cause harm. For example, significant progress is being made in the expression of opioid biosynthesis pathways in yeast (see https://doi.org/10.1007/s11101-019-09644-w). While production levels are not significant enough to influence the illegal drug market, such capabilities may soon be within reach. Likewise, enzyme pathways that synthesize harmful non-peptide toxins are also not directly harmful, but could foreseeably be engineered to produce dangerous toxins. -List-based approaches to bounding SOCs are limited to what is currently known to cause harm. To future-proof sequence screening, USG should encourage the development of homology and/or functional prediction approaches that could be used to determine whether a previously unknown sequence constitutes an SOC (e.g., http://doi.org/10.1128/iai.00334-21). -The final Revised Guidance should be intentional about the extent to which it focuses on sequences causing mass harm vs those that may cause harm to individuals. Both are important and have far-reaching implications on public perception and acceptance of biotechnologies, but differentiating might facilitate the determination of screening floors, ceilings, and/or other tiers or designations. 2.2 Database development The proposed Revised Guidance suggests the development of a database of SOCs. Developing a widely adopted SOC database would require significant (and ongoing) time, effort, and

resources. For widest adoption, such a database could be developed and maintained by an international organization independent of USG but be recognized by USG as being compliant with Guidance to enable US provider adoption. USG direction on the following considerations would be crucial to database development: -Tiers: A low tier comprised of FloorSOCs would enable non-screening companies to quickly implement screening against sequences of greatest concern. This tier would contain SOCs for which the source toxins and agents are well known, enabling transparency that can maximize uptake and support peer review/testing. The transparency and availability of this database tier would support norm building across the industry. Other tier(s) might have more restricted access, containing an expanded repertoire of SOCs with great capacity to cause harm that have not been published or that might not be obvious to a non-expert. These tier(s) could also include synthetic sequences designed to help catch obfuscated sequences or functional patterns. The engaged community of providers using this tier could also work toward its constant improvement. Providers might find it useful if Guidance suggested appropriate follow-up for different tiers, i.e., there may be tiers for which no follow-up is necessary, but that might be useful to store as a yellow flag (e.g., transcription factors influencing SOC expression, toxin biosynthetic enzymes). -Thresholds: Sequences exist at every step between the extremes of clearly dangerous and clearly benign, so USG guidance around appropriate database SOC thresholds would be very useful for database development. -Agility: A database might be more widely implemented if users are able to adjust parameters. For example, a SOC from an agent that is endemic in a given region may require less scrutiny there than in regions where the agent is absent. Level of concern of a given sequence will also be application specific, e.g., gene drives vs viral assembly. A database must also be rapidly adaptable to emerging threats. -Housekeeping genes: A workshop participant suggested that even housekeeping genes from regulated organisms might raise concern, not because of the sequences themselves, but because of the inferences that might be made about the customer's use. The participant suggested that there are few reasons to order housekeeping genes from pathogens unless one is trying to reconstruct a pathogen genome (see http://doi.org/10.1089/hs.2020.0004). False positives could be minimized if providers truly limited their screening to the single best match. Others suggested that housekeeping genes from pathogenic agents should not raise concern and rather should be kept on an "allowlist" to avoid triggering provider follow-up. -Genomic context: Many sequences are concerning only in given contexts, e.g., when other proteins are present

to form a complex or complete a pathway or network. Annotated SOCs within a database could incorporate information on the context effects that increase concern. However, significant research is needed in this area (more in Part 2 submission). -Information hazards: -Some workshop participants expressed a belief that databases should be 100% open considering that: -sequence information sufficient to start a global pandemic is publicly available. -the threat space is vast; unsequenced SOCs abound in the global environmental ecosystem and -pathogenesis and toxicity are context dependent: with a given host, environment, and expression level, all kinds of sequences can become concerning, therefore trying to hide all concerning sequences does not reduce threat but does limit opportunities for testing and improving the database. -Others felt strongly that some or all database information should be restricted, describing how a fully automated, highly secure screening system that is sensitive to sequence function, that encrypts sequence and customer information, and that is freely available to companies could enable rigorous screening without generating information hazards. -Providers expressed that a database with such access restrictions would complicate decision-making and communication for flagged orders. Customers generally do not appreciate the follow-up screening process, and this interaction could be further strained if a provider is unable to say why an order was flagged. -A need was also expressed for biosecurity evaluators to see the sequence annotation and any contextualizing information from the database to accurately assess the concern of a flagged sequence. In addition to better customer communication and decision-making, this also supports database curation as false positives are identified and understood. -Database security: Ideally, an international organization responsible for the database would be free to determine and implement appropriate, but not excessive or prohibitive, security measures. A database is not of use if providers cannot access it and if it cannot be kept up-to-date with input from many stakeholders. It’s important to note that many providers have made significant investments in their own screening systems and databases and would be unlikely to adopt something new. Actionable guidance should therefore be available to enable such providers to ensure the robustness of their own unique systems. (Non-profit, PPP)

20. Part 2: Introduction The issuance of proposed Revised Guidance for the DNA synthesis industry is laudable and of utmost importance to a safe, secure, and productive biological research ecosystem capable of addressing the great societal challenges of this time. We hosted an NSF-supported workshop with key stakeholders across the

industry as a forum for discussion and debate around elements of a robust Guidance framework. A “Part 1” submission responded to two elements of oligo screening that are central to the proposed Revised Guidance and that were considered at length during our workshop: 1) customer screening and responsibilities; and 2) sequence screening: sequences of concern. This “Part 2” submission addresses 3) sequence screening: technical considerations; 4) the sequence screening ecosystem; 5) benchtop synthesis equipment; and 6) emerging technologies. Risk cannot be eliminated from biological research and development, so we appreciate the care with which USG is working to balance the very real imperative to fervently support research with the implementation of security measures that are appropriate for the hazard space. We hope that our comment will be useful in the development of final Revised Guidance. 3: Sequence Screening: Technical Considerations 3.1 Technical details -Expansion from dsDNA to include ssDNA and RNA: This is feasible, implementable, and welcome guidance that will increase security. -With respect to RNA, it might be useful to consider that not all synthetic RNA is used to synthesize proteins. Small interfering RNAs (siRNAs), CRISPR guide RNAs (gRNAs), micro RNAs (miRNAs), etc, are active molecules by themselves that can affect DNA sequence and/or gene expression within an organism. Segments of these RNAs that are designed to bind to complementary target sequences would point to intended use, but such segments can be as short as 17 nucleotides and contain surrounding elements (e.g., PAM sequence) that would complicate screening. In considering how to approach screening for these RNAs, the difference in security concern between replicating sequences in an organism's genetic code and sequences with other activity might be considered. -Smaller screening window for non-batch orders (from 200 to 50 bp): At our workshop, there was broad, general consensus around the capability to detect 50 bp SOCs; however there are significant tradeoffs in asking providers to do this. A 50 bp window will increase the required compute power and increase false positives, thereby increasing provider costs. State of the art screening platforms can minimize these burdens, but those come at their own costs. Overall, USG should balance the risk posed by 50 bp sequences with the capacity for provider follow-up and the tolerance of customers for follow-up screening. If the number of false positives increases, provider follow-up will decrease in quality and customer tolerance may be diminished, potentially pushing customers to non-screening providers. If the risk posed by 50mers is high enough, then perhaps a 50 bp window is appropriate. If 50mers do not pose enough risk to warrant the burden on customers and providers, this window

should be reconsidered. Quantification of these risks could be undertaken and funded by USG to provide better data for making these decisions. 3.2 Batch orders Workshop attendees indicated that the attention given to batch orders in the proposed Revised Guidance is appropriate to increase detection capabilities for small fragments that can then be assembled into longer SOCs. -The specific encouragement to screen constituents of batch orders of oligos can be approached in at least two ways: -Combinatorial screening with state of the art technology: This approach yields significant and increasing numbers of false positives as screening windows decrease from 40 bp. Thus a combinatorial screening approach is best used when oligos are 35-40 bp or longer. -A potentially less computationally intensive approach would be to conduct a “pre-screen” of oligo pools that looks only for some threshold of sequence overlap (e.g., 8, 10, or 15 bp) between a positive strand of one oligonucleotide and negative strand of a second. For those overlapping oligos, an algorithm could next calculate their Tm. If that preliminary screening identified overlapping oligos with similar Tms, that would be evidence of intent to assemble and would trigger further combinatorial screening. With this approach, the length of the oligos matters less than the length of the overlap; screening 20mers might be feasible with 15bp overlaps. However, assembly plans do not universally require uniform Tms, so prescreening on that basis might not be sufficient. -The 1 µmol quantity standard is unlikely to meaningfully increase security. Assembly is routinely accomplished with quantities below 1 µmol. Additionally, the differing capabilities of industry to synthesize pools at very low quantities (e.g., femtomoles vs nanomoles) would result in some organizations essentially needing to combinatorially screen all oligo pools while others rarely would do so. 3.3 Best match or equivalent: standards and metrics Proposed Revised Guidance notes that providers may choose to use screening approaches they deem equivalent or superior to Best Match. This recognition that alternative screening systems may be equal to or superior to Best Match is welcome. However, it highlights a missing element from the Guidance and screening ecosystem. There are no standards that define Best Match performance, and therefore no metrics that can measure an alternative approach against Best Match. Workshop participants indicated that standards and metrics would provide significant value to providers and meaningfully contribute to security. One workshop participant noted prior research that indicated that some DNA synthesis companies believed they were in compliance with Guidance, but in fact fell short. Another workshop participant pointed to the Genome in a Bottle Consortium hosted by NIST as a potential model for

bringing private and public sector experts together to develop standards and a conformity assessment mechanism. NIST has the expertise to support the development of such, but would need supporting, on-going resources. Alternatively, an existing non-profit, public-private partnership could be identified to lead this effort in the U.S. On a global scale, it could be beneficial for an international organization with a biosecurity and biosafety focus (e.g. International Biosafety and Biosecurity Initiative for Science (IBBIS), soon to be launched by NTI) to be involved or lead the development of standards and metrics to increase international adoption. It was further noted that the utility of currently available databases for Best Match are not fit for purpose; many records are misannotated or contain sequences of genetic tools. Metrics could incorporate rates of false positive and false negative findings against test sequence sets and evaluate capabilities for detecting obfuscated sequences. Metrics and evaluation standards would need to be regularly updated in response to evolving capabilities and concerns. The development of standards and metrics would necessitate some degree of biological red-teaming, pressure testing, and/or auditing ; nefarious actors may use sequence obfuscation or other methods to out-maneuver sequence screening methods. Metrics should be able to evaluate a system's capacity for identifying obfuscated sequences. Concerns about information hazards can emerge from these practices, but these can be minimized and contained. There is value in good actors identifying and attending to vulnerabilities before they can be taken advantage of by nefarious actors. 4: The Screening Ecosystem 4.1 Boosting Guidance compliance -Boosting compliance with carrots: Many have suggested boosting compliance by requiring public funds e.g. from NIH, NSF, etc be used to buy DNA only from Guidance-compliant providers. This would be a powerful incentive, though would have some implementation challenges: -Some organization or entity would need to certify compliance so that customers knew which providers to use. This would require standards and metrics (covered in submission Part 1). Alternatively, membership in IGSC could be sufficient, however IGSC does not test members' screening capabilities after initial membership, so strengthening IGSC membership requirements, minimally through testing screening systems over time, would greatly increase the potential impact of such an approach. -Individual institutions would need to know which providers were Guidance-compliant and ensure that orders were placed only with those providers. Current practices for buying oligos at academic institutions would make this challenging—any solution where individual oligo orders pass through procurement would create significant slow downs that researchers would deem

unacceptable. -Customer education would be needed. -Boosting compliance by removing obstacles: Providers might choose not to screen out of concern for disruptions to operations and the cost of building, implementing, and maintaining screening systems. Screening as a service by a third-party or the availability of readily adoptable screening platforms could diminish these obstacles. -Boosting compliance with sticks: -It was suggested that, because Select Agent and Export Administration Regulations have the force of law, USG could require providers who make gene-length products to demonstrate that they are not synthesizing and transferring/exporting regulated materials. -Companies without screening could be required to purchase liability insurance. This would require some measurement of screening performance and should only be considered in conjunction with the availability of resources to minimize the burden of implementing minimal (floor) screening. 4.2 International considerations -As evidenced by COVID-19, biological threats are not contained by international boundaries. Joint security exercises can build international commitment and competence. Funding for such initiatives is needed. -International screening brings up many questions including who decides what needs to be screened for and who has access to that information. There was general support for an international body to bring international stakeholders together to collaboratively build norms and best practices for a secure screening ecosystem. -Research and development in the life sciences is an international endeavor. Every choice or element of security measures within the United States should be considered within that broader context. The US can continue to lead, while collaborating/discussing these important issues with international counterparts. This can help ensure that the steps taken by USG are useful beyond our own borders to make everyone safer, more secure, and able to reap the benefits of a robust R&D ecosystem. 4.3 Follow-up screening Follow-up screening is challenging for providers as they attempt to suss out whether or not their customer might (deliberately or unintentionally) cause harm with the ordered sequences. These are important decisions that have to be made relatively quickly and with limited information. Additional training, specific best practices, example scenarios, etc would be of great use to industry. As examples, a customer might provide the name of a biosafety officer at their company, but how does a provider verify the credentials and trustworthiness of that person? How can or should a provider verify documentation of a start-up located outside the US? Should concerns be “alleviated” if the customer withdraws their order? What if they state an intent to order from a different provider due to frustration about the screening

process? What standard should be met for contacting an FBI WMD Coordinator? Some of these follow-up interactions might be smoothed by USG providing sample questions or statements to use with customers during follow-up screening. This would increase consistency across industry and give industry some top cover. As USG considers how it will define SOCs, it is appropriate to continually recognize that “concern” is not binary. Some SOCs are very concerning, others less so. As database tiers are considered, it might also be appropriate to consider follow-up tiers. For example, providers could follow-up immediately on any sequences in the most concerning tier. Sequences in “yellow” tiers could be flagged, but not triggered for follow-up unless associated sequences are also ordered. Or, if a given customer ordered some number of yellow flag orders in a given time frame, that could trigger follow-up. Here again, though, clear guidance on what constitutes and alleviates concerns would be needed. 5: Benchtop Synthesis Equipment The inclusion of manufacturers of benchtop synthesis equipment is an important addition to the proposed Revised Guidance. Benchtop synthesis has a unique suite of challenges, including whether sequence screening should always “phone home” to the manufacturer or if local screening on a synthesis device can provide sufficient security. 5.1 Benchtop customer screening The emphasis on robust customer screening by manufacturers of benchtop equipment is appropriate. A few points of clarification would enhance the usefulness of the Revised Guidance for manufacturers. - Customer legitimacy: Verifying legitimacy of a customer of a benchtop device might involve different evidence or standards than verifying legitimacy for purchasing a SOC. - Equipment “appropriate for [customer] needs:” What criteria or documentation demonstrate customer needs? If a customer wants to buy a device that has advanced capabilities that the manufacturer thinks the customer does not need and might not use, should a manufacturer encourage (or insist upon) an alternative model? -“Manufacturers and their Customers should implement mechanisms to track continuously the legitimacy of users of their equipment:” It is unclear if the manufacturer or the customer is ultimately responsible for this. It is also unclear if this statement refers to all equipment users. For example, if a new graduate student, scientist, or research assistant joins a laboratory that operates a benchtop synthesis machine, should they be tracked if they might occasionally use the synthesis device? If the manufacturer has the role of tracking legitimacy of users, does the customer have an obligation to report the legitimacy of new lab members to the manufacturer? Or should the lab provide the name of the user to the manufacturer, who would screen it? It might be more appropriate for manufacturers to

keep records of the legitimacy of Primary Users instead of all users as this would become a significant administrative burden that might not add significant security. Another option that would track use more than legitimacy is for users to authenticate before every run of the machine and for that data to be kept for eight years. The draft Revised Guidance also says that “If the customer indicates plans to produce SOCs,” the manufacturer should conduct prescreening. This language suggests that the manufacturer does not have a responsibility to ask customers if they intend to synthesize SOCs. If not directly asked, customers might not be forthcoming about potential SOC synthesis, especially if they do not have immediate plans to produce SOCs. And, current synthesis needs are not always indicative of future needs and projects. Thus, hinging prescreening on customer indication of a plan to produce SOCs might result in such prescreening being inconsistently applied, and more likely to be applied to customers who are already security conscious. Additionally, it is not clear what is meant by “prescreening mechanisms to determine legitimate use.” Therefore, uniform, rigorous customer screening, independent of stated equipment use intentions, might be most appropriate. 5.2 Benchtop sequence screening There was significant discussion at the EBRC workshop about whether or not sequence screening locally on a synthesis device could provide sufficient security, or if a “phone home” approach is necessary. Phone home approaches enable manufacturers to flag and potentially halt the synthesis of SOCs and/or scan for unusual patterns of synthesis. Screening algorithms and databases can be updated in response to emerging or diminishing concerns. However, some customers cannot, will not, or prefer not to purchase internet connected devices, so if Guidance-compliant manufacturers do not offer devices with local screening capabilities, customers might turn to non-compliant manufacturers that lack screening capabilities all together. Customers may avoid equipment that phones home out for various reasons, such as IP and cybersecurity concerns. Cybersecurity approaches that encrypt sequence information could be implemented, but customers would have to trust those approaches. Other customers around the world, e.g. at remote research stations or non-urban areas, might not have consistent high-speed internet access. Local screening systems, however, are generally less secure. They could be hacked or disabled without the manufacturer becoming aware. Updating a local screening system in response to emerging or diminishing concerns would be very challenging without internet connectivity, expensive site visits from manufacturers, and/or shipment of a drive with update capabilities. Revised Guidance could strongly encourage phone home

approaches, but recognize the market pressure companies face to offer local screening mechanisms. It could describe best practices that enhance the security of locally screening devices when a phone home device is not an option, for examples: -Manufacturers could ensure that organizations that purchase locally screening equipment have a biosafety and/or biosecurity officer who meets with the manufacturer and Principal User in advance of purchase and at intervals (e.g., annually, biannually) thereafter to discuss equipment use and anticipated SOC synthesis. The extent to which such a biosafety/biosecurity officer is responsible for overseeing the use of the device has significant implications that should be carefully considered. Institutional biosafety committees are trusted to oversee broad swaths of research that carry significant biosafety and biosecurity risks. However, it is unreasonable to expect such officials to have oversight of all sequences synthesized within their institutions. One potential security increasing measure is to require biosafety/biosecurity officers to enter a unique approval code when a SOC is identified via local screening. Additionally, biosafety/biosecurity officers at institutions around the world may have different policies and responsibilities. Verifying the qualifications and relevant role of a biosafety or security officer might pose a significant challenge. -Manufacturers could charge customers a fee for periodic site visits by the manufacturer to run analysis on the screening system and its records and to install software updates. -Locally screening equipment could require user authentication for each sequence synthesized. (This might also be appropriate for equipment that phones home.) Similar to providers conducting follow-up screening, manufacturers would benefit greatly from having clear language in the Revised Guidance that they might share directly with customers to explain screening and security processes. 5.3 Security over equipment lifetime The emphasis in the proposed Revised Guidance on tracking equipment through its lifecycle is very important. Closed loop systems, in which equipment is bought back by companies for refurbishment and resale would decrease the possibility of a customer reselling on a secondary market without customer screening capacity. Alternatively, manufacturers could stipulate in purchase agreements that potential resales must be reported to them for new customer screening. The temptation to circumvent this safeguard could be dampened by limiting the sale of proprietary reagents to registered customers. It may be prudent to make customers aware of relevant export control regulations to communicate the importance of adhering to resale procedures. 6: Responsiveness to Emerging Technology Biotechnologies are rapidly advancing that will present new obstacles to

synthetic oligonucleotide synthesis security. Research that can strengthen and support the Guidance is also being undertaken. Thus, USG should institute a structure that allows for regular review and, as necessary, update to the proposed Revised Guidance. 6.1 Technologies that might challenge Guidance -Recoding the genetic code: Researchers are developing orthogonal translation pathways that utilize non-canonical amino acids and/or other monomers to build non-canonical biopolymers. In some cases, just a few recoding events could avoid BLAST detection, but more frequently, a significant number of codons need to be reprogrammed to avoid detection by screening algorithms. Additionally, researchers are improving upon techniques to incorporate unnatural base pairs into DNA and transcribe it to RNA. These active areas of research will advance rapidly in the coming decade. Therefore, USG could support research to explore how/if/when these developments might challenge sequence screening and possible solutions. -Whole genome design and editing: The capability to make many very specific genomic edits and modifications simultaneously allows researchers to tap into the depths of genetic possibility and discovery. This technology has many use cases, such as engineering an organism to produce higher titers of a desired product through engineering of regulatory sequences, controlling gene expression, and optimizing protein function and pathways. These outcomes depend upon genomic context. As platforms for genome design and editing are currently available, Guidance should work to address best practices for these companies and customers. 6.2 Technologies that might strengthen Guidance Several emerging technologies might also be able to strengthen the ability of providers, customers, and other stakeholders to enact best security practices for synthetic DNA. One approach to help address concerns such as reagent switching on benchtop devices, sequence obfuscation, and genetic recoding is a pattern-based approach to sequence screening (https://doi.org/10.1109/TKDE.2015.2510010). Another important approach is functional annotation and prediction. AI/ML advances are enabling greater predictive capabilities for novel protein development. Those algorithms could be applied to ordered sequences without significant homology to known sequences to help identify novel SOCs. Finally, the importance of standards and metrics was described previously, but is noted here as an area that needs research and development support. A concluding thought Liability was an undercurrent that ran through much of the workshop, occasionally surfacing to direct discussion. It, of necessity, plays a role in shaping how different stakeholders think about screening, and the impact of those concerns should be acknowledged and taken

into account. While the motivations of all stakeholders are complex and multi-dimensional, they ultimately stem from a commitment to the responsible advancement of life sciences research and development; there is obvious room for common ground and compromise. Industry might advocate for greater specificity in the Guidance so that liability for product misuse can be better assessed based on demonstrated compliance. Guidance that clearly articulates the role of each stakeholder helps all understand and protect their interests into the future, and provides a backdrop for rational discourse where the government is a valued partner. If the Guidance is vague and open to interpretation, the burden of uncertainty and risk is shifted to the future economic and legal landscape. The vastness of the threat space and the tradeoffs between iron-clad security and progress of research might deter USG from providing the degree of clarity desired by industry. To some extent, avoiding Guidance overreach would be useful for encouraging all parties to comply. On the other hand, fear of overreach should not prevent stakeholders from identifying and implementing screening that will have the greatest benefit without slowing the ground-breaking research and development in the biosciences, based on a community model (as seen herein) where the government is a partner. Funding to explore liability possibilities and frameworks, potentially through table-top exercises and reports could be useful. (Non-profit, PPP)

21. We co-organized and presented at the recent EBRC (NSF-supported) workshop in San Francisco, CA June 2-3, 2022 concerning the draft revisions to the HHS Guidance. Our staff have read through the comments that EBRC will be submitting, and they capture well what was discussed at the Workshop. (State Government)

22. To the Office of the Secretary, Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services (HHS): This comment is in response to Notice published on April 29, 2022, titled Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides (87 Federal Register 25495). We are writing as organizers and members of a Technical Consortium for DNA Synthesis Screening, an international and multi-stakeholder group working to develop and disseminate a Common Mechanism for DNA synthesis screening, which will include affordable software for DNA sequence screening along with resources to support customer screening. We plan to beta test an initial version of the Common Mechanism later this summer within the Technical

Consortium and with close partners, including members of the International Gene Synthesis Consortium. Our deep technical and policy expertise in this topic area includes bioinformatics of DNA sequences, pathogen genomics, DNA synthesis industry practices, and international engagement among diverse life sciences stakeholders. The Revised Guidance described in the Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides makes several positive advances beyond the original 2010 HHS Screening Framework Guidance for Providers of Synthetic Double-stranded DNA. We support many aspects of this Revised Guidance including: • Expanding the guidance to include responsibilities for third-party vendors, research institutions, principal users, and end users. In our discussions within the Technical Consortium to develop a customer screening framework, we have found that it is difficult to depend solely on DNA providers to ensure safe and legitimate use of synthetic DNA. By assigning some responsibility to third-party vendors, institutions, and users, this Revised Guidance broadens the discussion and provides a useful basis for incorporating these additional stakeholders. • Expanding the guidance to include both DNA and RNA, as well as both single- and double-stranded oligonucleotides. • Expanding the guidance to include sequences as short as 50 nucleotides in length. We believe that screening sequences at this length can reliably determine if they are a match to a potential sequence of concern or are a best match to a regulated pathogen or toxin sequence. However, lowering the threshold for screening from 200 nucleotides (from the 2010 Guidance) to 50 nucleotides will greatly increase the number of oligonucleotides that are subject to screening and will expand the number and type of providers expected to adhere to the guidance. Given that screening is already considered economically challenging for DNA providers , this broader recommendation should be paired with additional resources, tools, and incentives for adherence. • Expanding the Revised Guidance to include batch orders of oligonucleotides. While we support this requirement in principle, it poses some practical challenges that the Revised Guidance should address. Specifically, the technical tools for screening batch orders of oligonucleotides are not fully developed, and the most effective methods are not yet clear. Rather than defining the characteristics of batch orders and the methods for screening them, the Revised Guidance should encourage the community to develop effective screening strategies and best practices. The U.S. government

should support research on this topic. • Establishing guidance for manufacturers of benchtop DNA synthesis equipment. We agree with the Revised Guidance recommendation that benchtop device manufacturers follow a similar framework to traditional DNA providers, which includes both customer screening and DNA sequence screening. However, the Revised Guidance should also include roles and responsibilities for institutions in the oversight of benchtop device users (including, for example, user authentication and secured access) and in ensuring that each sequence is screened so that oligonucleotides or DNA fragments representing potential biorisks are only provided to authorized users. The Revised Guidance offers a range of recommendations that highlight the challenges related to DNA synthesis screening. The core issue is the dual challenge of encouraging DNA providers, as well as manufacturers and vendors of benchtop synthesis equipment, who currently do not screen orders and/or customers to conduct such screening, while also improving screening best practices among responsible providers—i.e., the challenge of raising the 'floor'—or baseline—level of screening while also raising the 'ceiling.' In discussions among Technical Consortium members, we have determined that a baseline capability that can facilitate screening among current non-screeners should be: as unambiguous as possible for ease of use; defensible by including only regulated and export-controlled sequences; and reasonably transparent to garner trust. To maximize adherence with recommended practices, the Revised Guidance should define baseline screening practices while encouraging development of best practices. Some of the recommendations listed above, such as screening batch orders of oligonucleotides, could be listed as best practices rather than baseline requirements until better screening tools are developed. There are two areas in the Revised Guidance where a delineation between baseline and best practices would be particularly helpful: • Expanding the guidance to include "Sequences of Concern" that are not specific to regulated pathogens or toxins. Although we agree that biosecurity risks can arise from sequences that are not specific to regulated pathogens and toxins, the definition listed in the Revised Guidance is broad and scientifically ambiguous. This ambiguity requires expertise, time, and commitment to resolve, and the expanded definition will dramatically increase the number of sequences that are flagged for follow-up. The Revised Guidance should include this definition as a best practice rather than a baseline requirement. • Recommending

strict security measures for databases of Sequences of Concern. Although we recognize the potential for “information hazards” related to such databases, we believe that expanding baseline sequence screening practices to DNA providers who do not currently screen, particularly in an international context, will require that we prioritize trust and transparency where possible. After much discussion within the Technical Consortium, we have determined that a broader distribution of a biorisk database is appropriate when it is limited to established virulence factors from regulated pathogens or listed toxins that are already found in publicly available resources. Such a biorisk database forms the basis of our baseline Common Mechanism. The Revised Guidance should clarify that databases with a definition of sequences of concern that is limited in this way can be more transparently shared to facilitate a baseline level of screening. We support the use of additional security measures for advanced databases with a broader definition of sequences of concern, which incorporate expert curation efforts and/or sequences of concern that are not widely publicly recognized. Such advanced databases are more likely to be used in support of screening best practices among a more limited number of DNA providers. We applaud the U.S. government for releasing this Revised Guidance and opening an important, valuable discussion on these challenging topics. As the Technical Consortium moves forward with testing and dissemination of the Common Mechanism among DNA providers and manufacturers of benchtop DNA synthesis devices, we will continue to seek opportunities to coordinate and harmonize our approach with this new Guidance. (NGO).

23. Response to Screening Framework Guidance for Providers and Users of Synthetic Oligonucleotides Our Company is a Provider of synthetic oligonucleotides that are used by Customers, End Users, and Principal Users (Customers) primarily for research and for use in other downstream applications such as next-generation sequencing (NGS) or molecular detection using polymerase chain reaction (PCR). We have long taken an active role in biosecurity for over a decade. Overall, we applaud the decisions reflected in the Draft Updated Screening Framework Guidance and are grateful for the opportunity by the Assistant Secretary for Preparedness and Response (ASPR) to provide comments. We believe the following items will increase biosecurity accountability and enforceability: • Expanding the parties responsible beyond Providers to all persons and

organizations who work with or transfer sequences of concern. • The reduction from 200 bp to 50 bp (but not below 40 bp) for minimum length to screen. • The explicit support for methods other than BLAST using NCNIs databases to screen sequences. We also believe that the current draft guidance could be improved in four key areas: 1) As currently written, the definition of “sequence of concern” (SOC) is ambiguous, particularly where the scope applies to sequences found in organisms outside of the Commerce Control List (CCL) or the Australia Group common control list. As currently defined, one could interpret SOC to broadly mean that Providers should treat everything with ANY pathogenic or toxic potential as being sequences of concern. This broad, overly inclusive interpretation could hinder the critical work and competitiveness of Providers that wish to comply with the guidance. Conversely, such ambiguity could lead to a market advantage for companies and individuals who choose a less strict interpretation of an SOC. We understand that this guidance aims to allow the community to respond as rapidly as possible to emerging threats. We respectfully submit that a better, less burdensome approach may exist. Specifically, Providers should define and document their criteria for determining SOCs for those sequences derived from or encoding select agents and toxins or other items on the CCL, as well as other classes of sequences that an organization judges to be of concern. Such documentation can, and should, lead to broader discussions within the community and, eventually, new entries to CCL or the Australia Group common control list when appropriate. While we believe this to be an appropriate solution, it brings up the long-standing conundrum within the security community: how to ensure that Providers and Customers can screen sequences using a consistent methodology while preventing bad actors from exploiting that methodology. Non-BLAST based screening methodologies exist that are easy to disseminate but do not contain discreet lists of threats and are extremely hard to reverse engineer. We encourage ASPR to support the development, implementation, and adoption of such Non-BLAST based screening methodologies as standards for the community. Doing so will encourage public discourse about threats, provide a standard screening methodology, and limit bad actors’ ability to reverse engineer the methodology to evade screening. 2) Total molarity and size of an oligonucleotide order are not good metrics for gauging risk. A gene can be made with as few as a dozen long oligonucleotides. Scrutinizing orders that have many oligonucleotides, either by

count or by the total molar amount, is a poor and inconsistent risk indicator for several reasons. First, in our experience, most, if not all, DNA assembly methods do not require large amounts of input DNA, where thousands of unique oligonucleotides could still be under a micromole amount. Second, many orders that include large numbers of overlapping oligonucleotides are designed for methods that do not relate to assembly methods, such as NGS enrichment. We believe a better alternative is for Providers to work with their Customers to mitigate risk rather than relying on the total molarity or size of an order. 3) We also believe short oligonucleotide alignment is a poor method to detect potential threats. In silico prediction of assemblies of short oligonucleotides is a complex and poorly defined process that often leads to multiple possible solutions that may or may not be biologically relevant or of concern. Attempting to in silico assemble and screen the inferred alignment sequences from such orders dramatically increases the burden of compliance on Providers with little to no reduction in safety. A Provider should be able to determine when a SOC bears a strong risk for potential misuse and then, if necessary, perform a diligent follow-up screening process with the Customer, rather than attempting to hypothesize what the intent is from a collection of short sequences. 4) Finally, from a policy perspective, we caution the ASPR to consider potential ramifications of overly stringent guidance. Requiring Providers to screen single stranded sequences in addition to the current process of screening double stranded sequences will create an approximately twenty-fold increase in effort for Providers. For oligonucleotides, screening single stranded sequences and the inevitable Customer follow-up will result in significantly increased costs and delays for those Customers and Providers. For most oligonucleotides shorter than 100 bases, Customer expect that Providers manufacture and ship them in under 24 hours. Even small delays can affect Customers' decisions about where to purchase such materials. This puts Providers, like us, who wish to follow this voluntary guidance at a potential disadvantage. Overly stringent guidance could also lead to the transfer of production to manufacturing sites outside of the U.S., resulting in the loss of U.S.-based production and associated U.S. jobs, as well as the loss of domestic regulatory control. We suggest that the guidance contain actionable guidelines with more precise language. We also recommend that the ASPR, in coordination with other agencies such as the Bureau of Industry and Security (BIS), work with the Provider

community to develop, implement, and endorse specific tools and methodologies as standards to increase the consistency of screening and decrease inefficiencies from ambiguity in the guidelines and regulations that exist today. Working with entities such as the International Gene Synthesis Consortium (IGSC) and the Engineering Biology Research Consortium (EBRC) to develop and refine these tools would be an ideal place to continue the important and impactful work the ASPR and other entities have begun. Thank you again for this opportunity to provide feedback on this important process. (Industry)

24. These comments represent Biosecurity expertise in industry. Comments address individual categories in the updated guidance and a roll-up summary at the end: Expanding scope to include End-users: Shifting responsibility to end-user/customer in regards to providing upfront legitimacy documentation if SOCs are included has benefits and challenges in our view Benefits: • Security is a shared responsibility! • End-users ought to be aware of risks of their own work, and this provision promotes broader security awareness. Challenges/logistics to implementation • Industry will need infrastructure to collect, secure and document customer legitimacy information. Resources to help facilitate these processes would be useful to industry (granted the actual requirements to update infrastructure will be company specific). • Protocols will be needed to correlate documentation with sequence screening results • Industry will need resources to guide/educate customers on SOCs (what they are, how they are to be identified) and exactly what documentation customers should provide when submitting orders containing SOCs • We request that guidance be specific in required legitimacy documentation and promote the development of resources to educate customers on 1. Documentation requirements and 2. SOC definitions Sequences Of Concern Broader Definition: Benefits: • Function based concern is necessary to evaluate biorisk potential, esp as advanced technology incorporates novel sequences that do not match existing lists. Downsides of a secure DB hosted by government: • The SOC DB needs to be dynamic and flexible and as such cannot be hidden. The Biosecurity community ought to continue to curate the DB with additional sequences as they are discovered and add application specific annotation, to define both True and False Positives in context specific manner • SOCs will look different across sectors/applications • community input would be valuable to evolve SOCs • Biosecurity teams that evaluate matches of

customer sequence against the SOC DB need visibility into the DB, including annotation, in order to evaluate level of concern. Goal of industry ought to be for FP to outweigh TP, however, FPs cannot be assigned without information about the actual SOC that has been identified. • SOC definitions cannot be strict across all technologies that leverage synthetic oligonucleotides nor all sectors (eg medical, biomanufacturing, environmental, etc) Other input on SOC definitions • Tiered SOC definitions may help screeners make False vs True positive calls. Regulated sequences should always be restricted, however, other tiers ought to be application specific. • Context of sequence being evaluated will impact the level of concern: This is of particular concern to genome engineering, which ought to have a dedicated guidance at some point. In the nearer term, the HHS Guidance for the Oligonucleotide Synthesis industry is the prevailing guidance for the expanding genome editing/writing technologies. • Genomic context: • False positive potential: SOC genes that contribute to pathogenicity or toxicity in native organisms may not be a concern when inserted into benign organism, due to lack of pathway members. This will lead to burdensome FPs. • False negatives may result due to unpredicted pathway functionality changes due to genomic editing, particularly in iterative fashion. • Environmental / application context also impactful. Eg. Organism containing a sequence of concern may be in a gastrointestinal tract environment when epithelial cell invasion is of most concern or in the environment when stability and other enhanced functions may cause species imbalance or other concerns. Suggested Solutions to SOC evaluation context challenges: • We suggest resources become available to support the development of algorithms that can evaluate sequence in genomic, organismal, and environmental context. (This will be challenging and will require complex test datasets and a systems biology approach) • •We suggest government supported resources for tools to expand existing functional prediction tools (such as SeqScreen, UltraSEQ and other Fun GCAT models) to add context prediction capabilities. • Towards supporting the evaluation of SOCs that are synthesized towards use in genome editing and writing, we also suggest algorithms be expanded to enable evaluation of numerous edits (sequence changes including substitutions/insertions) across a genome. These algorithms will be computationally exhaustive to evaluate the biorisk potential of each organismal variant. • We encourage resources to forums and mechanisms for scientists to

convene and provide input to the SOCs DB with application specific examples, case studies, expanded annotation, etc Follow up Screening: • Provision of example scenarios and resources to aid industry s will be useful. Similar to the suggestion to aid customer provision of legitimacy documentation, we suggest the updated guidance support education of end-users, customers and in general, the public, in the need for research risk awareness and the purpose of Sequence Screening. Summary: • Shifting responsibility for legitimacy documentation to the end-user has benefits, however, industry would benefit from additional resources to help implement collection of legitimacy documentation: clearer guidelines on what the documentation should include AND the definition of a SOC • Customer/end user responsibility is a plus, however education resources are needed. • Expanding SOCs is needed, however, the SOC DB must be sufficiently transparent to enable flexibility and adaptability. • Algorithm and DB resources and community coalescing are needed to support SOC evaluation in different genomic, environmental and application environments. Thank you for your efforts in providing this guidance and for this opportunity to contribute! (Industry)

25. Executive Summary: While there may be a legitimate need for revising the current USG Guidance for Providers and Users of Synthetic Oligonucleotides, the current proposed changes raise significant scientific and security concerns. The revision includes a number of items that would cause a major impact on end users to quickly obtain sequences to perform research, manufacturer’s ability to process and deliver requests in a short timeframe, and substantial IT concerns with networked equipment. Specific comments below are categorized into science, security, intellectual property concerns, administrative, and editorial headings. Science: • Sequence of Concern (SOC) definition is overly broad. Suggested tools are somewhat arbitrary and subjective in identifying SOCs in a general sense, let alone for using the suggested tools for unmatched sequences. The term "oligonucleotide" is not useful. "Oligonucleotide" traditionally refers to 20-30 mers. With current technology one can purchase an entire synthetic gene. Scope of guidance should apply to all synthetic nucleic acids. Recommendation: change “oligonucleotide” to “synthetic nucleic acid” • To what degree would a gene need to increase pathogenicity or toxicity to be considered an “SOC”? Who is responsible for deciding if a sequence fits this category? Keeping an accurate and up to date list of

sequences of concern can be very labor intensive. • The notion for providers to develop a database that includes genes “involved in pathogenicity or toxicity” with other SOCs is a security risk and restrictive to the progress of general science and is ambiguous. • The revised guidance recognizes that such a database does not exist, making compliance and consistency extremely difficult. • Who determines if something has scientific merit? • Self-development by providers for “predictive bioinformatic algorithms” to determine if unmatched sequences may also be SOCs could introduce error and be faulty. By whom or how would these tools be validated? Security: • The suggestion for manufacturers to enable internet connectivity for the purpose of sequence screening, user authentication and “data logging” on equipment to be sold is excessive and infringes on proprietary information rights (IP) of users and entities. • Smart equipment that is networked and would force entities to open firewall ports for incoming and outgoing data which has the potential to create vulnerabilities and are likely incompatible with internal IT policies for most if not all entities. • Where and who would maintain the database of Sequences of Concern (SOC)? The existence of this database in a publicly available arena would be a significant vulnerability. This document recommends the creation of a database of Sequences of Concern but does not attribute responsibility for the creation of the database. The suggestion is that the federal government develop a database of sequences of concern, administered by the NIH Office of Science Policy that all manufacturers must use to screen oligonucleotide orders. This database will be based on the organisms in the Federal Select Agent Program, Commerce Control Lists, and organisms classified as Risk Group 3 or higher by the United States CDC, NIH, or USDA. • There is the suggestion that providers develop a database that includes genes. Would this not invite discrepancy if each Provider and Third-Party Vendor were to create their own database? Additionally, the document states there is a need to develop such a database, but that such a database “…should include establishing a security office, protocols, and personnel reliability program, based on an assessment of risk, to guide selection, implementation, and monitoring of cybersecurity and information security capabilities and protection. Measures should ensure database confidentiality and integrity (including user access controls and sequence encryption in transit and at rest) and compliance with applicable laws such that sequences of concern data are protected against unauthorized access,

exfiltration, or other use.” • Suggest consideration of an easily accessible ‘restricted foreign threats list of countries to which sale is prohibited (i.e. a ‘COC’ or ‘Countries of Concern’ list), perhaps paired with the database that allows search for SOC? Place access to all items to be checked in one place. • This process would only be applicable in the US. What mechanism/efforts are in place to prevent/screen international orders? How are those manufacturers and providers ensured to follow these same requirements? Customer screening - 3rd Paragraph, https://www.federalregister.gov/d/2022-09210/p-59 - Shouldn't the list of regulatory and statutory prohibitions include a review of countries? This is likely captured under the last sentence in the paragraph referring to the Department of Commerce but if so, then "countries" should be included in the list in the first sentence. Consider adding "countries" to first sentence if these are a measure of restricted parties in the Departments listed. • The revised guidelines have considered various issues related to screening framework, including how individuals might circumvent the safeguards in place. The discussion ends up becoming a resource for how to circumvent existing and future safeguards in place. While it, consider future iterations leave out essentially a road map for how to circumvent safeguards. For example, how to distribute batch orders. • Consider the physical security of SOC materials. Encourage/describe development of a security plan to prevent theft of SOC. Intellectual Property Concerns • “Retain screening documentation of all hits for at least 8 years, even if the order was deemed acceptable. Retain records of any follow-up screening, even if the order was ultimately filled, for at least 8 years.” This raises the question of protecting intellectual property, especially for those orders that were deemed legitimate. Proposed increase in digital recordkeeping as well as suggestions to build data tracking into equipment introduce significant security risks (vulnerability as manufacturers and synthesizers are responsible for handling and storing an enormous amount of private and potentially sensitive information). • Sequence Screening Methodology - Last paragraph, https://www.federalregister.gov/d/2022-09210/p-55 - Encouragement is given to develop secure mechanisms to respect Intellectual Property. More weight to safeguard this information at the vendor site would encourage greater compliance with this draft guidance. • Recommendations - Manufacturer’s list, bullet 3: https://www.federalregister.gov/d/2022-09210/p-49 - Enabling Manufacturer to

screen sequences over the internet at a Customer's location appear to foster the ability to capture intellectual property from the User. How will the Manufacturer commit to securing intellectual property of the User obtained by documenting the oligos synthesized? Is this addressed elsewhere? (See https://www.federalregister.gov/d/2022-09210/p-55)? • How do providers develop “secure mechanisms designed to respect privacy, security, commercial, Intellectual Property, and other concerns” while at the same time develop methods to detect SOCs that may be broken up among multiple providers/vendors, or among multiple orders over a period of time to evade screening? Screening procedures already look for patterns. this would be extremely difficult to put into practice without compromising the privacy of the user. Administrative: • One reviewer specifically communicated with infectious disease researchers (customers) regarding this revised guidance for screening. The researchers expressed concern that additional burden not be added to the customer screening process, i.e. proving that they are legitimate research because it can negatively impact legitimate research projects. • The definitions provided in this revision (2022) has expanded on the previously existing definitions as well as adding new definitions, which helps clarify roles and define applicable materials. • “Customers, Principal Users, and End Users who know that their synthetic oligonucleotide order contains SOCs are encouraged to preemptively provide information that will assist the Provider or Third-Party Vendor in verifying their legitimacy”. There is concern that without a centralized and updated database Customers, Principal Users, and End Users would lack the tools to reliable provide this information. • Most times, individual that "originates" the order is either a laboratory manager or the end user. It is not the PI. This document seems to blend the two. Suggestion: Change as follows, "Principal User: The individual that conceptualizes the order or synthesizes oligonucleotides themselves and oversees the use of ordered or synthesized sequences in the laboratory. The Principal User may also be the End User. • Revised guidance recommends that transfers of SOCs, from Principal Users to End Users, and from Third-Party Vendors to Principal Users and End Users, are reported to the original Customer, such as the Institution that originated the order. This would be incredibly resource intensive to accomplish and would be detrimental to collaborations. • Institutions may not have “business practices in place” to accomplish the screening and recordkeeping practices

outlined, and the policy may be contrary to their current best practices. • Current recordkeeping practices may not extend to 8 years. This length of time increases burden for entities and could open them up for increased attempts to steal the information. Are sequences no longer potentially harmful or of concern after 8 years? Select Agent regulations require 3-year record retention. This disconnect could lead to unintended lapses in recordkeeping. • How would this be documented? Who would maintain these records? Institutional roles are very unclear. Who is the responsible party, particularly at research entities, to ensure this is followed? While this is proposed as guidance, what is in place to strongly encourage compliance? Specify responsible parties at User locations, Vendors, etc. to see that this guidance is followed and what entity, at some point, may review the records specified? • What will happen, or should happen, if safety or biosecurity concerns are identified? What is the process for reporting? Following up - https://www.federalregister.gov/d/2022-09210/p-61 - Is there a process available for someone in the lab to inform a biosafety officer or other individual if Malintent is suspected by the Principal or End User? It would be good to encourage entities to have some internal processes available for a person to report biosecurity concerns in a safe manner. • Is there a separate set of records to be kept by the biosafety officer? The document states a Providers and Third-Party Vendors should “notify Customers and Principal Users when their order contains SOCs.” Is the biosafety officer or “equivalent” notified? The biosafety officer would not necessarily be aware that a user was ordering an oligonucleotide. • What is an accepted “equivalent” for a biosafety officer in this context? Not all entities that would have need to order oligonucleotides have a requirement to have a biosafety officer. The recordkeeping and proactive proof of “peaceful, legitimate” research places a burden on all researchers, extending well beyond those engaged in research on select agents or SOCs . This would also place a significant burden on biosafety offices, or their equivalent, to provide proactive proof. • How would machine manufacturers ensure ‘customer legitimacy’ for the sale of their machines as users could misrepresent themselves or their research objectives? How would manufacturers track the ownership lifecycle for their equipment sold? • What are the criteria for determining legitimacy? What criteria are used for screening for a legitimate, bona fide, and peaceful purpose? Is there an appeal process if the Provider or Third-Party Vendor determines the research is not

legitimate? Are users able to try another Provider or Third-Party Vendor in the hopes that it will be approved, or is a database of denied orders to be maintained, and also required to be searched? • Who is responsible to ensure that all participants in this activity are educated on this guidance? Both at the level of the DHHS and internally at the entities involved? Editorial • First instance of SOCs being mentioned does not describe the term. Page 25496/1st Column. • Summary, https://www.federalregister.gov/d/2022-09210/p-3 - Summary, last sentence - Sentence could be strengthened. Add to the listed harmful result of misuse in the sentence to be more targeted. Add to text: "to bypass existing regulatory controls, commit unlawful acts, {and remove / negate) biosecurity." • Introduction - Paragraph 2, https://www.federalregister.gov/d/2022-09210/p-9 - Clarify sentence. It seems to state that "Individuals with no…need should be prevented from accessing …materials that could contribute to pathogenicity or harm…" Without the adjectives it seems to be clearer. The "and" confuses the meaning. Modify text to clarify - Change text to read: "Individuals with no legitimate, (no) bonafide, (nor) peaceful need should be prevented from …" • Goals - Sentence 2, https://www.federalregister.gov/d/2022-09210/p-27 - Remove potential misunderstanding that targeted sequences must be from organisms regulated by both FSAP and CCL and are not covered if only regulated by one or the other. Semantics are often offered as justification why regulations were not followed. Change "and" to "and/or" to ensure capture of item that may not yet have made both lists. Change text to read "… transfer is regulated by FSAP (and/or) CCL." • Recommendations - First list: Bullet 4? https://www.federalregister.gov/d/2022-09210/p-36 - In the federal register website of document, the fourth statement bullet is not the same square bullet as the others in the list, as seen in the PDF. Not sure if change is required or simply a quality review of the change from the PDF to the website text. • Recommendations - Manufacturer's list, bullet 3: https://www.federalregister.gov/d/2022-09210/p-49 - Similar bullet issue as above. Bullet 3 in wrong format. (NGO)

26. The HHS draft guidance does not describe the responsibility and accountability of the governmental authority in ensuring compliance across both manufacturers and research-based customers. The HHS draft guidance instead apparently shifts responsibility for biosecurity surveillance to manufacturers, including the

development of novel databases to anticipate potentially concerning sequences that are related to pathogenicity and toxicity. Lastly, the HHS draft guidance apparently introduces a new level of control over research organizations, again shifting compliance primarily to manufacturers, with encouragement to customers to facilitate orders by providing information establishing the legitimacy of their research. Custom oligonucleotide synthesis service organizations already have established practices in place to screen new orders for a match to Sequences of Concern, at least for longer (>50nt) sequences. The ability to screen shorter fragments ordered in 1 micromolar quantities, as defined in the HHS draft guidance, will present manufacturers with an incremental bioinformatics burden and with a challenge in vetting new research organizations who order such products. Custom oligonucleotide manufacturers also benefit from the existence of an industry trade association that facilitates the biosecurity policy objectives with customer and Sequence of Concern screening protocols. The burden is much more substantial for manufacturers of oligo synthesis instrumentation. In our case, if the HHS draft guidance were to take full effect, significant design changes of our existing commercial inventory of research use instruments to enable the internet connectivity and electronic record storage capability specified in the guidance would have to take place. To our knowledge, this area of manufacturing does not have an equivalent trade association that would facilitate compliance. Ultimately, biosecurity compliance responsibility for these oligo synthesizing instruments lies with the end user: as such, it appears the requirements on instrument manufacturers creates an excessive burden. Established diagnostic assay manufacturing customers of our custom oligonucleotide synthesis service have expressed concern that their own exploratory research on pathogenic and toxic sequences may suffer extended order lead times. This inefficiency would stem from the oligo synthesis manufacturer vetting a new use of Sequences of Concern for research purposes using fluid and relatively undefined criteria. The effect on new, unvetted customers who seek to establish novel technologies for exploratory research programs on pathogens and toxins is uncertain, but there is some concern that such vetting and surveillance activities by oligo synthesis manufacturers may have a chilling effect on that kind of research. The specific areas that would benefit from clarification by HHS are: 1.) Definition of the statutory authority within which the HHS draft guidance is being offered and the

proposed mechanism for HHS to check implementation by manufacturers. a.) Without that regulatory context, manufacturers are unable to assess the business risk posed by partial or ineffective implementation of the requirements. b.) Other cabinet-level departments –Commerce and State – define types of manufactured products that may pose biosecurity risks and procedures to be used for product registration, classification, and licensing as appropriate. c.) There is currently no obvious Department charged with the surveillance and tracking of US-based research organizations that use custom made oligos. This apparently new authority should be defined by HHS. 2.) Definition of the scope of the proposed guidelines: a.) Will the draft guidance apply to orders that originate outside the US and are fulfilled in LGC's European custom oligo manufacturing sites? b.) Will LGC Biosearch Technologies be obliged to track and report customer qualifications and orders globally? 3.) Definition by HHS of Sequences of Concern and related sequences that must be screened by manufacturers. a.) This aspect is left for manufacturers and/or trade organizations to develop in the HHS draft guidance. b.) If the related sequences of potential concern are left undefined, however, the guidance will be implemented in a non-standard way across the industry, limiting its effectiveness. c.) Novel databases for sequences of potential pathogenic or toxic concern should be developed by HHS, not by manufacturers (Industry)