UNITED STATES DEPARTMENT OF COMMERCE
Bureau of Industry and Security
1401 Constitution Avenue, Suite 3896
Washington, DC 20230

September 25, 2023 22-25

[redacted]

Dear [redacted]:

I am responding to your March 11, 2022, email transmitting a request for advisory opinion from the Bureau of Industry and Security (BIS) pursuant to 15 CFR § 748.3(c) of the Export Administration Regulations (EAR) on behalf of the [redacted]. The [redacted] letter asked BIS some broad questions regarding the interpretation of the genetic elements controls under Export Control Classification Number (ECCN) 1C353 and requests guidance on several examples of specific questions that might help delineate the scope of the control.

First, the letter asked BIS to define the word "gene" within the context of Export Control Classification Number (ECCN) 1C353 as the term is not defined within the text of the ECCN or in the "Definitions of Terms" in Part 772 to the EAR. The word "gene" can have a variety of definitions depending on the practical or technical context of its use and BIS is currently considering whether and how to provide public guidance.

The [redacted] letter also asked BIS to provide guidance on the length of sequence that would constitute a gene, noting the 2010 Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA published by the U.S. Department of Health and Human Services recommended a matching length of 200 nucleotides (nt) as a threshold for screening sequences. BIS does not provide a length threshold for classification since the lengths of gene sequences can vary widely. Additionally, some genes can be significantly truncated and still produce a fully functional protein while others may lose function with removal or substitution of only a single nucleotide. BIS assumes the translated product to be functional unless the exporter can provide conclusive evidence demonstrating a loss of function. An example of this interpretation is provided in the answers to the seven specific hypotheticals presented by the [redacted] as follows:

1) If a customer orders 75% of an open reading frame of a protein, does this still constitute a gene? *The [redacted] believes this will still require an export license since function may be preserved, unless data exists that demonstrates loss of function in the shortened sequence. Were such data to exist we believe the companies should maintain documentation from the customer describing the relevant loss of function.*

Unless the manufacturer or exporter provides conclusive evidence to demonstrate the protein product is not functional, BIS would assume the product to be functional and classify a fragment with 75% coverage of a controlled genetic element ECCN 1C353.

2) If a customer orders 75% of a hypothetical or predicted protein, does this constitute a gene? *The [redacted] believes that orders for shortened ORFs from unannotated proteins should not require a license given that no realistic risk estimate is possible for the shortened sequence and no known function has been demonstrated*.

As long as the hypothetical or predicted proteins are not "specific to," or share homology with a gene encoding a protein of a virus listed on the Commerce Control List (CCL) or a protein associated with pathogenicity of a controlled bacterium or fungus, BIS would not consider these elements to code for a gene and would designate these genetic elements as EAR99. Items designated EAR99 generally do not require a license to most destinations, end uses, or end users that are not listed in parts 744 or 746 of the EAR.

3) If a customer orders a full-length sequence but significantly changes or disrupts a region that makes up a key functional domain shown to be necessary for protein function does this still constitute a gene? *The [redacted] believes this should not require an export license but that companies should maintain documentation from the customer describing the relevant inactivation.*

4) If a customer orders a full-length sequence that encodes a gene that would be subject to a license requirement but incorporates specific point mutations documented in literature to disable the biological function of the encoded protein, does this still constitute a controlled gene? *The [redacted] believes, given that biological function is not preserved, that this should not require an export license but that companies should maintain documentation from published literature describing the effects of these mutations.*

The responses for questions 3 and 4 in the letter are the same: A genetic element that otherwise meets criteria for control under ECCN 1C353 but is known or demonstrated to be incapable of performing any biological function would be designated EAR99. Record keeping of orders of any sequences that flag as "sequences of concern" is consistent with the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA published by the U.S. Department of Health and Human Services, regardless of whether a BIS export license is required.

5) If a customer orders a sequence that is a 'best match' to a gene from a regulated species but does not have high homology (say, 60% homology vs. the controlled protein sequence), does this still constitute a controlled gene? *The [redacted] believes, absent evidence to the contrary, that a best match should still determine controlled status, regardless of the degree of match.*

BIS recommends screening of sequence orders all open reading frames against protein amino acid sequences. Provided the best match is to a protein that is specific to a controlled organism

and that translated sequence is not demonstrated to lose function due to the sequence divergence, BIS would maintain ECCN 1C353 classification in the situation described here.

6 If a customer orders a sequence from a gene that would be subject to a license requirement but breaks these sequences up into short (e.g., 300 base pair) segments with homologous overlapping sequences, *and* indicates to the synthesis provider that they intend to assemble these sequences into a longer construct, does the collection of these sequences constitute a controlled gene subject to a license requirement? *The* [redacted] *believes that a customer indicating an intent to assemble sequences would trigger a license requirement.*

BIS agrees that such a scenario presents a red flag. Intentionally manipulating an order for purposes of avoiding the license requirements in the EAR is itself a violation of the regulations as described in § 764.2 of the EAR. BIS strongly suggests that the exporter ask the customer to provide documentation of the legitimate business reason for breaking up the sequences into shorter segments that do not have a license requirement, when both exporter and customer know that the license requirement exists for longer segments, and that the customer intends to reassemble the sequences. If the customer cannot sufficiently document the reason for the exporter, then the exporter should either decline this transaction or submit a license application to BIS for the transaction anyway. Exporters should review the BIS Red Flag and Know Your Customer guidance on the BIS website: https://www.bis.doc.gov/index.php/all-articles/23-compliance-a-training/47-know-your-customer-guidance.

7) If a customer orders a sequence that encodes a portion of a viral polyprotein, should the polyprotein itself be considered the gene or should the post translationally cleaved elements within the polyprotein be considered the gene? If the latter, should unannotated regions of the polyprotein and those regions that contain peptides that are unlikely to be large enough to be functional be considered "genes"? *The* [redacted] *believes post translationally cleaved elements from a polyprotein that are shown to be functional proteins should be considered genes if the size of the gene is 66 amino acids or greater. Unannotated regions of a viral polyprotein, regions involved in cleavage, and this annotated as peptides with fewer than 66 amino acids should not be considered genes.*

BIS considers the final, post translationally processed products to be the basis of the "genes" in this case. Fragments of the polyprotein sequence that are unannotated could not reasonably be considered "genes," as it is not possible to identify the functional product of those elements. BIS would control the genes for any of the individual proteins or peptides, irrespective of amino acid sequence length.

The [redacted] letter also requested BIS guidance on classifying highly pathogenic avian influenza (HPAI) viruses. BIS concurs with the interpretation indicated by the [redacted] specifically that, absent pathogenicity data demonstrating high pathogenicity, all strains that are not identified as H5 or H7 and all H5 and H7 variants lacking multiple basic amino acids within the hemagglutinin cleavage site should be designated EAR99.

Finally, the [redacted] requested clarification of the scope of the control for ECCN 2B352.j for automated nucleic acid synthesizers and assemblers and how this applies to gene synthesis service providers using multiple machines for production of their products. BIS intended the technical parameters in ECCN 2B352.j to capture stand-alone, automated systems that can generate full length genes in a single run. This would not include manually operated systems comprised of multiple, non-integrated instruments. Software classified under ECCN 2D252 is intended to capture software capable of performing the full "design to build" function on a single platform classified as ECCN 2B352.j, therefore; if the instrument is not classified under ECCN 2B352.j, then the related software is not controlled under ECCN 2D252 and would be designated EAR99.

BIS wishes to express our sincerest appreciation for the thoughtful questions and scenarios presented by [redacted]. As you are aware, we are constantly reviewing and modifying our controls, particularly in the sphere of biotechnology, to optimize the balance between export controls related to national security and open and robust commercial trade. Inquiries like yours are one of the more useful tools for refining and focusing our guidance to the export community.

In rendering this opinion, BIS has relied upon the information provided in the [redacted] letter transmitted to BIS[redacted]. Any change in the facts and circumstances, as presented in your letter and restated in this advisory opinion, may implicate different regulatory obligations, including potential licensing requirements, under the EAR. If you have questions with regard to any aspects of this advisory opinion, please contact Dr. Wesley Johnson, Microbiologist in the Bureau's Chemical and Biological Controls Division at Wesley.Johnson@bis.doc.gov.

Sincerely,

THEODORE CURTIN

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Ted Curtin, Director
Chemical and Biological Controls Division