DEPARTMENT OF COMMERCE

Bureau of Industry and Security

15 CFR Part 774

[Docket No. 220826-0174]

RIN 0694-AI84

Request for Comments Concerning the Imposition of Section 1758 Technology Export Controls on Instruments for the Automated Chemical Synthesis of Peptides

AGENCY: Bureau of Industry and Security, Commerce.

ACTION: Advance notice of proposed rulemaking (ANPRM).

SUMMARY: The Bureau of Industry and Security (BIS), Department of Commerce, maintains controls on the export, reexport and transfer (in-country) of dual-use items and less sensitive military items pursuant to the Export Administration Regulations (EAR), including the Commerce Control List (CCL). Certain instruments for the automated synthesis of peptides (automated peptide synthesizers) have been identified by BIS for evaluation according to the criteria in section 1758 of the Export Control Reform Act of 2018 (ECRA) pertaining to emerging and foundational technologies. BIS is seeking public comments on the potential uses of this technology, particularly with respect to its impact on U.S. national security (e.g., whether such technology could provide the United States, or any of its adversaries, with a qualitative military or intelligence advantage). This advance notice of proposed rulemaking also requests public comments on how to ensure that the scope of any controls that may be imposed on this technology would be effective (in terms of protecting U.S. national security interests) and appropriate (with respect to minimizing their potential impact on legitimate commercial or scientific applications).

DATES: Comments must be received by BIS no later than **[INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]**.

ADDRESSES: You may submit comments, identified by regulations.gov docket number BIS-2022-0023 or by RIN 0694-AI84, through any of the following:

- *Federal eRulemaking Portal: http://www.regulations.gov*. You can find this advance notice of proposed rulemaking by searching for its regulations.gov docket number, which is BIS-2022-0023.
- *E-mail*: PublicComments@bis.doc.gov. Include RIN 0694-AI84 in the subject line of the message.

All filers using the portal or e-mail should include the name of the person or entity submitting the comments in the name of their file(s), in accordance with the instructions below. Anyone submitting business confidential information should clearly identify the business confidential portion at the time of submission, file a statement justifying nondisclosure and referring to the specific legal authority claimed, and provide a non-confidential submission to be made publicly available.

For comments submitted electronically containing business confidential information, the file name of the business confidential version should begin with the characters "BC." Any page containing business confidential information must be clearly marked "BUSINESS CONFIDENTIAL" on the top of that page. The corresponding non-confidential version of those comments must be clearly marked "PUBLIC." The file name of the non-confidential version should begin with the character ''P." The "BC" and "P" should be followed by the name of the person or entity submitting the comments or rebuttal comments. Any submissions with file names that do not begin with a "P" or "BC" will be assumed to be public and will be made publicly available through *https://www.regulations.gov*.

FOR FURTHER INFORMATION CONTACT: For questions on automated peptide synthesizers, contact Dr. Tara Gonzalez, Chemical and Biological Controls Division, Office of

Nonproliferation and Treaty Compliance, Bureau of Industry and Security, Telephone: (202) 482-3343, E-mail: Tara.Gonzalez@bis.doc.gov. For questions on the submission of comments, contact Willard Fisher, Regulatory Policy Division, Office of Exporter Services, Bureau of Industry and Security, U.S. Department of Commerce, (202) 482-6057, E-mail: RPD2@bis.doc.gov.

SUPPLEMENTARY INFORMATION:

Background

Identification of Section 1758 Technologies

As part of the National Defense Authorization Act (NDAA) for Fiscal Year 2019, Public Law 115-232, Congress enacted the Export Control Reform Act of 2018 (ECRA), 50 U.S.C. 4801-4852. Section 1758 of ECRA (as codified under 50 U.S.C. 4817) authorizes the Bureau of Industry and Security (BIS) to establish appropriate controls on the export, reexport or transfer (in-country) of emerging and foundational technologies essential to the national security of the United States. Due to the absence of specific definitions or other guidance in ECRA differentiating the terms "emerging technology" or "foundational technology," and in order to ensure greater efficiency in implementing controls for such items, BIS has chosen to characterize such technologies as "Section 1758 technologies" for purposes of section 1758 of ECRA, rather than characterizing a specific technology as either "emerging" or "foundational."

As described in section 1758(a)(2)(B) of ECRA, the identification of Section 1758 technologies takes into account: (i) the development of these technologies in foreign countries; (ii) the effect export controls imposed pursuant to this section may have on the development of such technologies in the United States; and (iii) the effectiveness of export controls imposed pursuant to this section on limiting the proliferation of the emerging and foundational technologies in foreign countries.

The Secretary of Commerce must establish appropriate controls on the export, reexport or transfer (in-country) of technology identified pursuant to the Section 1758 process. In so doing,

the Secretary must consider the potential end-uses and end-users of Section 1758 technologies, and the countries to which exports from the United States are restricted (e.g., embargoed countries). While the Secretary has discretion to set the level of export controls, at a minimum a license must be required for the export of such technologies to countries subject to a U.S. embargo, including those countries subject to an arms embargo.

In addition, section 1758(a)(2)(C) of ECRA (50 U.S.C. 4817(a)(2)(C)) requires the interagency process for identifying Section 1758 technologies to include a notice and comment period.

November 19 Advance Notice of Proposed Rulemaking

On November 19, 2018, BIS published an advance notice of proposed rulemaking, "Review of Controls for Certain Emerging Technologies" (83 FR 58201) (November 19 ANPRM). The November 19 ANPRM identified biotechnology in a representative list of fourteen technology categories concerning which BIS sought public comment to determine whether there are specific emerging technologies that are essential to U.S. national security and for which effective controls can be implemented. The biotechnology-related comments submitted to BIS in response to its November 19 ANPRM are not addressed in this ANPRM, because none of the comments specifically addressed the question of export controls on automated peptide synthesizers.

Evaluation of Automated Peptide Synthesizers pursuant to Section 1758 of ECRA

Instruments for the automated synthesis of peptides (automated peptide synthesizers) have been identified by BIS for evaluation according to the criteria in section 1758 of ECRA pertaining to emerging and foundational technologies.

Peptides and polypeptides are polymeric chains of amino acids, linked together by peptide bonds. Proteins are three-dimensional (3D) macromolecules composed of one or more folded large chains of polypeptides. Proteins must fold into the correct 3D shape to be functionally active. The first peptide bond was synthesized over 100 years ago. However, in the

last few decades, advances in chemical synthesis methods have established automated peptide synthesis as a common laboratory technique.[1] Long-established synthesis methods using fluorenylmethyloxycarbonyl (Fmoc) chemistry can reliably and routinely produce high quality polypeptides around 50 amino acids in length.[2]

Recent advances in peptide synthesis technology and instrumentation have increased both the speed of peptide synthesis and the length of peptide products, including peptides and proteins greater than 100 amino acids in length.[3] Most protein toxins that are controlled under Export Control Classification Number (ECCN) 1C351 on the Commerce Control List (CCL) (see Supplement No. 1 to part 774 of the EAR) are over 100 amino acids in length and have an average length of 300 amino acids (with the notable exception of conotoxins, which range between 10-100 amino acids in length). Consequently, absent the imposition of additional controls on the export, reexport or transfer (in-country) of certain peptide synthesis technology and instrumentation (e.g., automated peptide synthesizers), there would be an increased risk that such technology and instrumentation could be used to produce controlled toxins for biological weapons purposes.

Request for Comments

Consistent with section 1758(a)(2)(C) of ECRA (50 U.S.C. 4817(a)(2)(C)), BIS welcomes comments on the following questions. If specific automated peptide synthesizer instruments are described by respondents, BIS requests that this should be done, to the extent practicable, within the context of the following questions.

(1) What is the current state of development of automated peptide synthesizers in the United States, including those having primarily academic or commercial applications, and how does this compare with that of other countries (e.g., is the United States at the forefront of such

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[1] R.B. Merrifield, *Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide*, 85 J. Am. Chemistry Soc'y 2149 (1963).
[2] Da'san M. M. Jaradat, *Thirteen Decades of Peptide Synthesis: Key Developments in Solid Phase Peptide Synthesis and Amide Bond Formation Utilized in Peptide Ligation*, 50 Amino Acids 39 (2017).
[3] Sameer S. Kulkarni et al., *Rapid and Efficient Protein Synthesis Through Expansion of the Native Chemical Ligation Concept*, Nature Revs. Chemistry, Mar. 29, 2018, at 1.

development in the academic and commercial fields)? Where possible, please identify any publicly available studies that support your position.

(2) What is the current availability and predominate application(s) of automated peptide synthesizers in the United States and how does this compare with that of other countries (e.g., how common is the use of these instruments in life sciences laboratories/institutions and other academic or commercial settings)?

(3) To what extent are custom peptide synthesis services available in the United States and other countries, and would the availability of such services (particularly for academic or commercial applications) be likely to impact domestic or foreign demand for automated peptide synthesizers?

(4) To what extent are current or near-term developments in peptide synthesis technology expected to address the challenges of peptide length, sequence fidelity, and protein folding (e.g., are efforts currently underway to integrate protein folding into the automation process)?

(5) To what extent would the establishment of Section 1758 technology export controls on automated peptide synthesizer instruments, and related "software" and "technology," impact U.S. technological leadership in this field (e.g., within the academic or commercial spheres) and would this impact be distinctly different if controls were placed primarily on "software" as opposed to hardware, or *vice versa*?

(6) To what extent would the imposition of Section 1758 technology export controls on automated peptide synthesizer instruments, and related "software" and "technology," likely be effective in terms of limiting the proliferation of these items abroad (including the potential use of such items to produce controlled toxins for biological weapons purposes)?

(7) To what extent has the increased availability of lower cost coupling reagents, together with recent advances in automated peptide synthesizers and related technology, overcome economic or technological factors that previously might have limited the availability and use of this technology, abroad?

(8) To what extent should Section 1758 technology export controls on peptide synthesizer technology be implemented multilaterally (rather than unilaterally), in the interest of increasing their effectiveness and minimizing their impact on U.S. industry?

Several respondents who commented on BIS's November 19 ANPRM indicated their preference for multilateral export controls over unilateral export controls, because the former typically place U.S. industry on a more level playing field with respect to producers/suppliers in other countries. In this regard, note that section 1758(c) of ECRA (as codified under 50 U.S.C. 4817(c)) provides that "the Secretary of State, in consultation with the Secretary [of Commerce] and the Secretary of Defense, and the heads of other Federal agencies, as appropriate, shall propose that any technology identified pursuant to subsection (a) [of ECRA] [which addresses the interagency process for identifying Section 1758 technologies] be added to the list of technologies controlled by the relevant multilateral export control regimes."

Finally, BIS encourages comments addressing any other automated peptide synthesizer technology topics deemed to be relevant to this inquiry.

Comments should be submitted as described in the ADDRESSES section of this ANPRM and must be received no later than **[INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]**.

This ANPRM has been designated a "significant regulatory action," although not economically significant, under Executive Order 12866. Accordingly, this ANPRM has been reviewed by the Office of Management and Budget (OMB).

Matthew S. Borman,

Deputy Assistant Secretary

for Export Administration.

[FR Doc. 2022-19430 Filed: 9/12/2022 8:45 am; Publication Date: 9/13/2022]