Small Business Innovation Research (SBIR) and
Small Business Technology Transfer (STTR)
Opportunity Announcement
HR001120S0019-10
Flexible Manufacturing of Fine Chemical Reagents

Which program will fund this topic?
SBIR
What type of proposals will be accepted?
Direct to Phase II (DP2) Only

Technology Area(s): Biomedical, Chemical/Biological Defense, Materials/Processes
DARPA Program: Make-It

I. INTRODUCTION

The Defense Advanced Research Projects Agency (DARPA) Small Business Programs Office (SBPO) is issuing an SBIR/STTR Opportunity (SBO) inviting submissions of innovative research concepts in the technical domain(s) of Biomedical, Chemical/Biological Defense, Materials/Processes. The National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health is a partner agency on this SBIR. DARPA and NCATS are interested in exploring the feasibility of developing U.S.-based manufacturing capabilities for critical fine chemical reagents. DARPA is most interested in approaches that flexibly address fine chemical manufacturing across a variety of products that includes pharmaceuticals; NCATS is most interested in approaches that specifically address fine chemical manufacturing for pharmaceutical products.

This SBO is issued under the Broad Agency Announcement (BAA) for SBIR/STTR, HR001120S0019. All proposals in response to the technical area(s) described herein will be submitted in accordance with the instructions provided under HR001120S0019, found here: https://beta.sam.gov/opp/b8abeb02f16a4450b2c2f859fc00c177/view.

a. Eligibility

The eligibility requirements for the SBIR/STTR programs are unique and do not correspond to those of other small business programs. Please refer to Section 3.1, Eligible Applicants, of HR001120S0019 for full eligibility requirements.

b. Anticipated Structure/Award Information

Please refer to Section 1, Funding Opportunity Description provided in HR001120S0019 for detailed information regarding SBIR/STTR phase structure and flexibility.

If a proposer can provide adequate documentation to substantiate that the scientific and technical merit and feasibility described in the Phase I section of the topic has been met and describes the potential commercial applications, the Direct to Phase II (DP2) authority allows the Department of Defense (DoD) to make an award to a small business concern under Phase II of the SBIR program without regard to whether the small business

concern was provided an award under Phase I of an SBIR program. This SBO is accepting DP2 proposal submissions.

DARPA will accept DP2 proposals for cost of up to $1,750,000. This includes a 24-month base period not to exceed a cost of $1,000,000 and a 12-month option period not to exceed a cost of $500,000. A separately priced option of up to $250,000 must also be proposed for contractors who would like to be considered for participation in the DARPA Entrepreneurial Investigator Initiative. Refer to Section 2.6, DARPA Embedded Entrepreneur Initiative, of HR001120S0019 for detailed information on EEI.

Proposers should refer to Section 4, Application and Submission Information, of HR001120S0019 for detailed proposal preparation instructions. Proposals that do not comply with the requirements detailed in HR001120S0019 and the research objectives of this SBO are considered non-conforming and therefore are not evaluated nor considered for award.

DP2 Feasibility Documentation shall not exceed 15 pages. DP2 Technical Proposal shall not exceed 40 pages. Phase II commercialization strategy shall not exceed 5 pages. It should be the last section of the Technical Volume and will not count against the 40-page limit. Please refer to Appendix B of HR001120S0019 for detailed instructions on DP2 proposal preparation.

c. Evaluation of Proposals

Section 5, Evaluation of Proposals, in HR001120S0019 provides detailed information on proposal evaluation and the selection process for this SBO.

d. Due Date/Time

Full proposal packages (Proposal Cover Sheet, Technical Volume, Price/Cost Volume inclusive of supporting documentation, and Company Commercialization Report) must be submitted via the DoD SBIR/STTR Proposal Submission website per the instructions outlined in HR001120S0019 no later than **2:00pm ET, June 29, 2020.**

II. TOPIC OVERVIEW

a. Objective

Develop a U.S.-based manufacturing capability for critical fine chemical reagents.

b. Description

Fine chemicals are generally defined as those produced in lower quantity (<1M kg/yr) and at higher price (>$10/kg) than commodity chemicals. Since the 1970s, production of such products has shifted from the U.S. to overseas, and today China's chemical industry is 2.5x larger than that in the U.S. based on total sales [1]. This shift has left the U.S. vulnerable to supply chain disruptions due to global events that include trade embargoes, natural disasters and, as recently demonstrated, pandemics. Although shortages of critical finished products such as pharmaceuticals have received much attention due to supply chain disruptions, including those related to COVID-19, developing U.S.-based

production capabilities for these products is ultimately dependent on availability of small molecule reagents (<700 Da) that are also produced offshore. While any supply disruption is problematic, certain key reagents are even more critical as they are utilized as starting materials for many different products. For example, substituted pyrroles are common in a broad range of finished chemical products as illustrated by a select set in Figure 1. Shortages of fine chemicals with many endpoints have the potential to cause simultaneous disruptions across healthcare, energy, construction and other sectors.

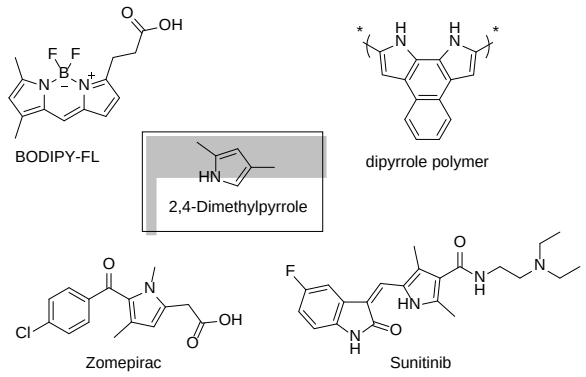

Figure 1. Diverse products with pyrrole starting material spanning pharmaceuticals, electronics, and dyes

One challenge in building fine chemical redundancy is the large number and variety of substances that are used in chemical manufacturing. Commodity chemicals, produced in >1M kg/yr quantities, comprise the largest segment of chemical production by mass but represent fewer than 100 different types of molecules. In contrast, tens of thousands of fine chemicals are used to manufacture products including drugs, dyes, material coatings, fuel additives, pesticides and batteries. Though there are many factors that result in offshore production, commercial incentives to build production capacity and dedicated production lines/facilities for a single or even a few fine chemicals are typically low considering ultimate market volume.

Recent demonstrations [2-3] in the DARPA Make-It program provide a promising approach to this challenge that minimizes required infrastructure and maximizes synthetic flexibility of a given production line. Make-It has demonstrated fully automated, reconfigurable small molecule synthesis platforms that are capable of producing nearly all of the World Health Organization's essential drugs using three to five solution-based reactions, at production scales up to 1 g/hr on a single device. While such devices are appropriate for synthesizing fine chemicals with minimal manual intervention by chemists and/or operators, they are not currently capable of meeting the scale required to meet industrial demand.

Scale and diversity of product are important within a single, reconfigurable device to rapidly address supply chain interruptions as they arise. DARPA is most interested in approaches that flexibly address fine chemical manufacturing across a variety of products that includes pharmaceuticals; NCATS is most interested in approaches that specifically address fine chemical manufacturing for pharmaceutical products. This SBIR will

support a small business to build the techno-economic analysis, business plan and physical production platforms to flexibly produce critical fine chemicals at sufficient scale that could rapidly augment supply at a nation-wide level when needed. These systems should be designed with maximum synthetic flexibility in mind to ultimately support a long-term, dynamic business strategy. However, in order to demonstrate initial commercial viability, proposers should identify one or more critical products reliant on fine chemicals produced offshore that inform selection of more than four fine chemicals on which the system will be demonstrated.

c. Phase I

This SBO is accepting Direct to Phase II proposals ONLY. Proposers must demonstrate that the following has been achieved outside of the SBIR program: Construction and operation of a flexible and/or modular, automated approach to chemical synthesis that produces multiple reagents. Systems of most interest are those that have already demonstrated synthetic capability and/or complexity aligned with relevant fine chemicals. System operation should scale from 1-100 g/day with minimal change in final platform cost and/or mass of product generated. Feasibility documentation should support the product specifications described in this paragraph and may consist of patent applications, patents awarded, research reports from externally funded research, research reports from internally funded research, and refereed scientific or technical publications.

d. Phase II

Performers will:

- Provide the intended fine chemical target list, justify importance of targets selected for demonstration and provide projections for system synthetic flexibility across a larger set (>30) of molecules, including a mapping of targets to end product(s). Starting materials should meet the definition of "commodity" chemicals as defined above. Emphasis should be on synthetic simplicity and flexibility to produce many fine chemicals from a common set of commodity chemicals with on-board process monitoring.
- Produce at least four fine chemicals that have been identified as starting materials for important chemical products. Purity specification should meet appropriate requirements for finished product manufacturing or >98%, whichever is greater.
- Demonstrate system reconfiguration (manual or automated), including all cleaning, in less than four hours.
- Demonstrate system scalability from 1-1000 g/day equivalent with minimal change in final platform cost and/or mass of product generated.

i. Schedule/Milestones/Deliverables Phase II fixed milestones for this program should include:

- Month 6: Demonstrate modular synthesis of at least two fine chemical targets from commodity starting materials; switch between targets in <6 h, including cleaning and system reconfiguration.
- Month 10: Demonstrate scalability (>100 g/day) of two fine chemical targets.

- Month 12: Draft techno-economic analysis and business analysis, including projections of platform flexibility across fine chemical targets and final end product(s).
- Month 18: Demonstrate modular synthesis of at least four fine chemical targets from commodity starting materials; switch between two targets (unique from Month 4 milestone) in <4 h, including cleaning and system reconfiguration.
- Month 22: Demonstrate scalability (>1000 g/day) of four fine chemical targets within six days; Finalization of techno-economic analysis and business plan.
- Month 24: Final deliverables: 1. Analysis of fine chemical production, including cost/kg to produce demonstrated targets at multiple scales; 2. Technical details for construction, including list of parts and system design(s); 3. Report on operation, including operating procedures; 4. Techno-economic analysis and business plan, including analysis for demonstrated targets and broader projected accessible targets mapped to end-state application.
- Month 25: Deliver device specifications, including designs, blueprints and/or production/manufacturing plans for the first generation system with proposed enhancements for improved performance (e.g., usability, automation, throughput, etc.) in future generations.
- Month 30: Produce improved prototype device that integrates second generation components included advanced features such as automated target selection, simplified (semi-automated) device cleaning, standardized connections for module expansion, etc.
- Month 33: Deliver report on device production costs (materials, manufacturing, etc.) for scales ranging from 10-1,000 devices. Ensure adherence to manufacturing standards and protocols for producing selected target products.
- Month 36: Deliver final prototype device including analysis of consumer safety features, energy consumption and durability.

e. Dual Use Applications (Phase III)

The ability to flexibly produce important chemical reagents at fixed marginal cost will improve national readiness with respect to supply chain disruptions. It will also benefit normal business operations by allowing companies to respond more quickly to unforeseen market disruptions. Further funding is therefore likely from both government and commercial sources.

f. References

[1] 2020 Facts and Figures. European Chemical Industry Council. Retrieved from cefic.org/app/uploads/2019/01/The-European-Chemical-Industry-Facts-And-Figures-2020.pdf

[2] Coley et al., Science, 2019, 365(557), eaax1566 DOI: 10.1126/science.aax1566

[3] Bettenhausen, C., C&EN News, 2020, 98(5) retrieved from cen.acs.org/business/instrumentation/AI-robotics-come-together-synthesis/98/i5

g. Keywords

Chemistry, Continuous Manufacturing, API, Pharmaceuticals, M*aterials*

III. SUBMISSION OF QUESTIONS

DARPA intends to use electronic mail for all correspondence regarding this SBO. Questions related to the technical aspect of the research objectives and awards specifically related to this SBO should be emailed to HR001120S0019@darpa.mil. Please reference BAA HR001120S0019-10 in the subject line. All questions must be in English and must include the name, email address, and the telephone number of a point of contact.

DARPA will attempt to answer questions in a timely manner; however, questions submitted within seven (7) calendar days of the proposal due date listed herein may not be answered. DARPA will post a consolidated Frequently Asked Questions (FAQ) document. To access the posting please visit: http://www.darpa.mil/work-with-us/opportunities. Under the HR001120S0019-10 summary, there will be a link to the FAQ. The FAQ will be updated on an ongoing basis until one week prior to the proposal due date.

In addition to the FAQ specific to this SBO, proposers should also review the SBIR/STTR General FAQ list at: http://www.darpa.mil/work-with-us/opportunities?tFilter=&oFilter=29934. Under the HR001120S0019 summary, there is a link to the general FAQ.

Technical support for the Defense SBIR/STTR Innovation Portal (DSIP) is available Monday through Friday, 9:00 a.m. – 5:00 p.m. ET. Requests for technical support must be emailed to DoDSBIRSupport@reisystems.com with a copy to HR001120S0019@darpa.mil.