

REQUEST FOR INFORMATION

*Off-the-shelf Continuous Crystallizer*

May 31, 2017

Enabling Technologies Consortium™

Request for Information

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# Introduction

## About Enabling Technologies Consortium™ (ETC)

The Enabling Technologies Consortium™ (ETC) is comprised of pharmaceutical and biotechnology companies collaborating on issues related to pharmaceutical chemistry, manufacturing, and control with the goal of identifying, evaluating, developing, and improving scientific tools and techniques that support the efficient development, and manufacturing of pharmaceuticals. The purpose of this consortium is to identify pro-actively high-value opportunities to deliver innovative technologies where the business case is compelling and collaboration with the broader external community is required.

## Request for Information

Publication of this Request for Information (RFI) is the first step by ETC to gather information on and solicit interest in collaborating together on an Off-the-Shelf Continuous Crystallizer on a future ETC project (expected 2018). The information collected during the RFI process will be used to inform plans for future ETC projects. As noted below, responses to RFIs should contain only high level discussions of product development efforts and should not contain trade secrets or confidential information. Respondent(s) to this RFI may be invited to submit a proposal to a future Off-the-Shelf Continuous Crystallizer RFP (expected 2018).

The RFI process will serve to provide ETC members with information on project scope, timeline, and resource requirements in order for ETC to define the 2018 Project Roadmap and allow individual ETC members to meet budget allocation deadlines to support projects in 2018.

## Disclaimer

The contents and information provided in this RFI are meant to provide general information to parties interested in developing an Off-the-shelf Continuous Crystallizer. If a collaborative project results from this RFI, the successful respondent will be required to execute an Agreement that will govern the terms of the project. When responding to this RFI, please note the following:

* This RFI is not an offer or a contract
* Proposals submitted in response to this RFI become property of ETC
* Respondents will not be compensated or reimbursed for any costs incurred as part of the RFI process
* Any questions received from potential respondents will be anonymized and made available to all respondents via our website
* All proposals received in response to this RFI will remain confidential within ETC and not shared with other respondents
* Responses to RFIs should contain only high level discussions of product development efforts and should not contain trade secrets or confidential information
* ETC is not obligated to contract for any of the products and services described in this RFI
* ETC reserves the right to:
  + Accept or reject any or all responses
  + Waive any anomalies in proposals
  + Negotiate with any or all respondents
  + Modify or cancel this RFI at any time

## RFI Contact Information

All questions and inquiries regarding this RFI should be directed to:

Ms. Alexis Myers

Project Coordinator

ETC Secretariat

c/o Drinker Biddle & Reath, LLP

1500 K St NW

Washington DC, 20005-1209

(202) 842-8800

[info@etconsortium.org](mailto:info@etconsortium.org)

<http://www.etconsortium.org/>

## Anticipated Time Frames for Evaluation and Selection Process

Issue RFI May 30, 2017

Questions on RFI due June 14, 2017

Responses to RFI due July 12, 2017

Initial 2018 ETC Project Roadmap defined Oct. 2017

Notification of Next Steps Oct./Nov. 2017

*The initial 2018 ETC Project Roadmap will be defined at the ETC Board of Directors meeting in October 2017. Following that meeting, all respondents will be informed of next steps related to the Off-the-Shelf Continuous Crystallizer Project.*

***Please submit your response electronically to the above address. Responses received after July 12, 2017 will not benefit from full consideration and may be excluded from the selection process.***

# Project Information

## Possible Project Sponsors

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| AbbVie, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, BMS, Eli Lilly, GSK, Merck & Co., Pfizer, Takeda |

## Description

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| Off-the-shelf continuous crystallizers are not commercially available. The current approach is to custom-build equipment using readily available parts from different 3rd parties. There are many disadvantages to the custom-build approach:   * There is no detailed approach on exact details of what to build. The custom-build approach is time-consuming and logistically difficult to plan. * Equipment sustainability: Hardware and software maintenance over time can be challenging. * Variability in approaches, equipment sizes, parts, data logging and control software can lead to observations that are user-specific and may not necessarily create learnings useful to the scientific community in general. * Variability in what is deemed “all necessary and salient process data” to make process design and troubleshooting decisions from.   This project will be conducted in collaboration between ETC and the selected 3rd party. Throughout the duration of this project, ETC and the 3rd party will work together to develop the desired Continuous Crystallizer platform. ETC will supply the selected 3rd party with a comprehensive list of requirements, subject matter expertise, and funding to support this project. The selected 3rd party will supply the resources and expertise to design, prototype and ultimately produce a continuous crystallizer laboratory reactor skid. Upon completion of the project, it is anticipated that the continuous crystallizer will be made available to the scientific community as a commercialized product. |

## Off-the-Shelf Continuous Crystallizer Requirements

### Necessary Hardware and Software Requirements

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| **Hardware**   * Ability to work with crystallizer sizes (50-1000 mL), types, baffles, stirrer types/mixing elements. * All components would be modular with multiple configurations, drop-in vessels and simple connections between components with options to purchase vessels and parts from multiple vendors. * The equipment will be a complete system to study continuous crystallization rather than merely a communication interface connected to custom-built flow equipment. * Ability to produce mass rates from 10 g/d to 1000 g/d and suitable to replicate equipment for manufacturing scale. * Vessels transfer fluid using options as seen appropriate without affecting the physical properties of the slurry.   + It is not a requirement (nor an expectation) that the transfer of slurries between vessels be truly continuous (i.e., discretized transfer in “slugs” could be acceptable if properly managed). * Ability to easily control the reactor temperature ranging from at least -20 to 100°C, stirring rate, inlet/exit flowrate, recycle ratio, residence time and throughput, metering in solids. * Manual sampling from the reactor(s) should also be easily achievable. * The materials of construction for the reactor and transfer lines should be suitable to accommodate concentrated acids, bases, aggressive organic solvents, and temperature ranges. * Ability to generate supersaturation by cooling, anti-solvent addition, salt formation, salt breaking (via acid/base addition) and evaporation. * Ability to nucleate the system via seeding, sonication and high-shear wet-milling or add a third party device with industry standard communication protocols. Nucleation devices need to be able to turned on and off according to user-input timing sequences. * Ability to add or remove residence time easily (via adding/removing modular units), add multiple measurement points, and multiple anti-solvent points. * The exit stream contents should be representative of the bulk reactor contents and the transfer streams need to remain fully suspended. * Feed lines and transfer lines need temperature control. Feeds and transfers can be with strictly continuous flow or intermittent batch transfers if performed at intervals that don’t impact process performance. * Ability to use controlled recirculation loops. * Ability to easily visualize the reactor geometry and its reactor contents, either through a view cell, wall/window or an in-situ process microscope. * All necessary instrumentation available including temperature, pressure, pH, RPM, flowrate.   Ability to use with at least two in-situ process monitoring tools with standard inlet sizes and fittings, or with an external loop.   * Couple with a holding tank (diversion) or a continuous-isolation laboratory skid (recovery).   Ability to control crystallizer headspace conditions, such as nitrogen inerting.   * Ability to fit the entire kit into a standard chemical fumehood, including plug and play with standard hood utilities (nitrogen, vacuum, heating/cooling fluid,…). * The equipment should be able to handle and transfer hazardous compounds (personal exposure of < 5 g/m3), be sealed, exhibit minimal solvent loss and allow for safe unmanned operations for at least 16 h. * The systems should also be designed for automated event notification and shutdown. * Replacement reactor parts lists should be readily available and options of who to buy from also easily available * Cleaning the equipment should not require significant effort. * A service contract should be available to maintain all equipment and software.   **Software**   * Ability to create an experimental control file that generates a raw data file and a report suitable for use as or incorporation into an electronic notebook and into company repositories. * Software should function within the constraints of the local IT requirements at each company. * Qualification should be provided for all controls/systems with specific calibration frequency. * Ability to export process data into standard formats (.txt, .csv,…) suitable for data processing and modeling tools. * Ability to easily merge data with standard process analytical technology tools offline. * Trending should include temperature, pressure, dosing, transfer rates. Control should be programmable or recipe driven, however, parameters or procedures can be changed during experimentation. * The software should invoke emergency shutdown procedures based on practical measures such as reactor temperature, reactor and wall temperature differential, pressure,… |

### Optional Hardware and Software Requirements

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| **Hardware**   * Ability to change feed flow and recycle addition points (sub-surface or above surface) * Exit streams and transfer line should handle slurries with up to 50% solid mass, particle size up to 500m) during transfer with minimal or no impact to the PSD. * Clean-in-place capability * Portable – the ability to assemble, disassemble and reassemble for moving and storage should not require chemical fumehood modifications or significant vendor support. * Use in a cGMP environment * Ability to recycle a solids-free (mother liquor) stream from exit stream back to inlet ports anywhere upstream or downstream * Ability to use in-situ or recirculation loops utilizing high shear dispersers and maintain temperature control.   **Software**   * Ability to easily merge process analytical technology tools data online with a vision to become Allotrope compliant. * Ability to integrate unit with higher level automation, such as DCS (distributed control systems). |

### Availability Requirements

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| * The expected output is a commercially available mixed-suspension mixed-product-removal crystallizer. Plug-flow or oscillatory-baffled reactors are also acceptable options. * Timing for development and availability can be negotiated. The vendor must be open to feedback on the roadmap to product delivery. |

### Licensing Requirements for Commercialized Product

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| * Commercially available continuous-stirred tank reactor. * IP is owned by the vendor. |

# Criteria for Evaluation

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| The ETC will evaluate the responses to this RFI based on the 3rd party’s ability to:   * Provide response with desire to participate in collaboration. * Meet the functional, performance, and technical requirements described in this RFI as evidenced by the RFI response and presentations made to ETC. * Provide a cost-effective solution that is compatible with the goals of the project. * Demonstrate domain expertise and an ability to work collaboratively with the ETC in development of the Off-the-shelf Continuous Crystallizer. * Provide a superior level of customer service and technical support, both pre-installation and post-installation to clients. * Discuss potential partnerships and current development efforts that show similarities to this request. * Provide any additional capabilities that may differentiate them from other potential collaborators.   The ETC will not be able to provide individual feedback to RFI respondents. |

# Respondent Profile *(to be completed by RFI respondent)*

Please provide information to the following:

## Company/Organization Information

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| --- | --- |
| Company/Organization Name |  |
| Address |  |
| City |  |
| State |  |
| Country |  |
| Zip Code |  |
| Website |  |

## Primary Contact Person

|  |  |
| --- | --- |
| Name |  |
| Title |  |
| Email address |  |
| Phone Number |  |

## Company/Organization Overview

Provide a brief overview of your company/organization including number of years in business, number of employees, nature of business, description of clients, and related products developed and commercialized to date.

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## Parent Corporation and/or Subsidiaries

Identify any parent corporation and or subsidiaries, if appropriate.

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## Summary of Expertise

Give a brief description of your company/organization’s expertise in the area/field related to this RFI. Include any experience working on projects with Consortia/Associations.

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## Standards Certifications

List any certifications currently held, including date received, duration, and renewal date.

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## Goals and Strategic Vision

Provide a summary of your company/organization’s short term and long term goals and strategic vision.

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## Miscellaneous

Please enter your response to each requirement using the guidelines provided in the tables below. If additional documentation or schematics are required to respond to a particular question, please answer the question as succinctly and accurately as possible and reference supplemental attachments.

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# Company/Organization Response to RFI (*to be completed by RFI respondent)*

## Proposal

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## Functional Requirements & Specifications

Refer to the following Functional Requirements and Specifications checklist which summarizes the collective requirements and specifications by the member companies participating in the project.

Based upon your proposed approach to deliver a solution, provide a response to each checklist item along with comments and assign one of the following Codes to each item:

|  |  |
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| A | Current capability of existing product |
| B | Able to add capability as requested |
| C | Able to add capability with modification to ETC request |
| D | Unable to add capability |

| Requirement | Code | 3rd party Comments |
| --- | --- | --- |
| **HARDWARE REQUIREMENTS** | | |
| Ability to work with crystallizer sizes (50-1000 mL), types, baffles, stirrer types/mixing elements. |  |  |
| All components would be modular with multiple configurations, drop-in vessels and simple connections between components with options to purchase vessels and parts from multiple vendors. |  |  |
| The equipment will be a complete system to study continuous crystallization rather than merely a communication interface connected to custom-built flow equipment. |  |  |
| Ability to produce mass rates from 10 g/d to 1000 g/d and suitable to replicate equipment for manufacturing scale. |  |  |
| Vessels transfer fluid using options as seen appropriate without affecting the physical properties of the slurry. It is not a requirement (nor an expectation) that the transfer of slurries between vessels be truly continuous (i.e., discretized transfer in “slugs” could be acceptable if properly managed). |  |  |
| Ability to easily control the reactor temperature ranging from at least -20 to 100°C, stirring rate, inlet/exit flowrate, recycle ratio, residence time and throughput, metering in solids. |  |  |
| Manual sampling from the reactor(s) should also be easily achievable. |  |  |
| The materials of construction for the reactor and transfer lines should be suitable to accommodate concentrated acids, bases, aggressive organic solvents, and temperature ranges. |  |  |
| Ability to generate supersaturation by cooling, anti-solvent addition, salt formation, salt breaking (via acid/base addition) and evaporation. |  |  |
| Ability to nucleate the system via seeding, sonication and high-shear wet-milling or add a third party device with industry standard communication protocols. Nucleation devices need to be able to turned on and off according to user-input timing sequences. |  |  |
| Ability to add or remove residence time easily (via adding/removing modular units), add multiple measurement points, and multiple anti-solvent points. |  |  |
| The exit stream contents should be representative of the bulk reactor contents and the transfer streams need to remain fully suspended. |  |  |
| Feed lines and transfer lines need temperature control. Feeds and transfers can be with strictly continuous flow or intermittent batch transfers if performed at intervals that don’t impact process performance. |  |  |
| Ability to use controlled recirculation loops. |  |  |
| Ability to easily visualize the reactor geometry and its reactor contents, either through a view cell, wall/window or an in-situ process microscope. |  |  |
| All necessary instrumentation available including temperature, pressure, pH, RPM, flowrate. |  |  |
| Ability to use with at least two in-situ process monitoring tools with standard inlet sizes and fittings, or with an external loop. |  |  |
| Couple with a holding tank (diversion) or a continuous-isolation laboratory skid (recovery). |  |  |
| Ability to control crystallizer headspace conditions, such as nitrogen inerting. |  |  |
| Ability to fit the entire kit into a standard chemical fumehood, including plug and play with standard hood utilities (nitrogen, vacuum, heating/cooling fluid…). |  |  |
| The equipment should be able to handle and transfer hazardous compounds (personal exposure of < 5 g/m3), be sealed, exhibit minimal solvent loss and allow for safe unmanned operations for at least 16 h. |  |  |
| The systems should also be designed for automated event notification and shutdown. |  |  |
| Replacement reactor parts lists should be readily available and options of who to buy from also easily available |  |  |
| Cleaning the equipment should not require significant effort. |  |  |
| A service contract should be available to maintain all equipment and software |  |  |
| **OPTIONAL -** Ability to change feed flow and recycle addition points (sub-surface or above surface) |  |  |
| **OPTIONAL -** Exit streams and transfer line should handle slurries with up to 50% solid mass, particle size up to 500m) during transfer with minimal or no impact to the PSD. |  |  |
| **OPTIONAL -** Clean-in-place capability |  |  |
| **OPTIONAL -** Portable – the ability to assemble, disassemble and reassemble for moving and storage should not require chemical fumehood modifications or significant vendor support. |  |  |
| **OPTIONAL -** Use in a cGMP environment  Ability to recycle a solids-free (mother liquor) stream from exit stream back to inlet ports anywhere upstream or downstream |  |  |
| **OPTIONAL -** Ability to use in-situ or recirculation loops utilizing high shear dispersers and maintain temperature control. |  |  |
| **SOFTWARE REQUIREMENTS** | | |
| Ability to create an experimental control file that generates a raw data file and a report suitable for use as or incorporation into an electronic notebook and into company repositories. |  |  |
| Software should function within the constraints of the local IT requirements at each company.  Qualification should be provided for all controls/systems with specific calibration frequency. |  |  |
| Ability to export process data into standard formats (.txt, .csv,…) suitable for data processing and modeling tools. |  |  |
| Ability to easily merge data with standard process analytical technology tools offline. |  |  |
| Trending should include temperature, pressure, dosing, transfer rates. |  |  |
| Control should be programmable or recipe driven, however, parameters or procedures can be changed during experimentation. |  |  |
| The software should invoke emergency shutdown procedures based on practical measures such as reactor temperature, reactor and wall temperature differential, pressure,… |  |  |
| **OPTIONAL -** Ability to easily merge process analytical technology tools data online with a vision to become Allotrope compliant. |  |  |
| **OPTIONAL -** Ability to integrate unit with higher level automation, such as DCS (distributed control systems). |  |  |

## Estimated Timeline

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## Estimated Project Cost

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