

REQUEST FOR INFORMATION

**Protein-Product Separation Technologies for Biocatalytic Reactions Utilized in Commercial API Manufacture**

January 25, 2023

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 is the first step by ETC to solicit interest in collaborating on the project titled **“Protein-Product Separation Technologies for Biocatalytic Reactions Utilized in Commercial API Manufacture.”** The information collected during this process along with subsequent interviews will be used for evaluation purposes. {Depending on the responses received ETC may choose to select a collaborator solely based upon its response to the RFI or may choose to refine project requirements and subsequently release a Request for Proposals (RFP) to aid in the collaborator selection process.}

## Disclaimer

The contents and information provided in this RFI are meant to provide general information to parties interested in developing the project **“Protein-Product Separation Technologies for Biocatalytic Reactions Utilized in Commercial API Manufacture.”** The successful respondent selected by ETC 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
* Responses submitted in response to this RFI become the property of ETC
* Respondents will not be compensated or reimbursed for any costs incurred as part of the RFI process
* If ETC receives and responds to questions from RFI respondents, ETC reserves the right to anonymize the questions and make the questions and ETC’s responses available to all respondents via our website
* Responses to RFIs should contain only high-level discussions of product development efforts and should not contain trade secrets or confidential information. ETC does not make any confidentiality commitments with respect to RFI responses but agrees not to publicly distribute RFI responses outside of ETC or share RFI responses with other respondents.
* ETC is not obligated to contract for any of the products or services described in this RFI
* ETC reserves the right to:
	+ Accept or reject any or all proposals
	+ Waive any anomalies in proposals
	+ Negotiate with any or all bidders
	+ Modify or cancel this RFI at any time

## RFI Contact Information

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

Ms. Fatou Sarr

ETC Secretariat

c/o Faegre Drinker Biddle & Reath, LLP

1500 K St NW

Washington DC, 20005-1209

202.230.5148

info@etconsortium.org

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

## Anticipated Time Frames for Evaluation and Selection Process\*

Issue RFI January 25, 2023

Questions on RFI due March 1, 2023

ETC responds to any RFI questions April 1, 2023

Responses from potential collaborators due May 1, 2023

*\*Dates subject to change without notice*

***Please submit your response electronically to the above address. Responses received after May 1, 2023 will not benefit from full consideration and may be excluded from the selection process.***

## Project Scoping and Project Execution

ETC project sponsors will work with the selected collaborator to define the project scope and work to finalize a Statement of Work (SOW) for the project which describes project timelines, milestones, budget, deliverables, etc. Depending on the project, the scoping exercise will be conducted via email, web-meetings, and/or an in-person workshop. Following finalization of the SOW, the project will be brought forward to the ETC Board of Directors to authorize moving to execution.

Once authorized by the ETC Board of Directors, the ETC Secretariat will work with the selected collaborator to negotiate and finalize a contract between the two parties, leveraging ETC’s Development Agreement and Non-Disclosure Agreement accelerator templates. In parallel to this negotiation, the Secretariat will also work to finalize and execute our internal project Charter between participating ETC members.

## Intellectual Property

ETC acknowledges that this project, or aspects thereof, may require the use and incorporation of existing intellectual property and/or the development of new intellectual property in order to successfully complete the project.

### Existing Intellectual Property

* ETC as an organization will not engage in negotiations with the owner of any intellectual property on the respondent’s or ETC’s behalf;
* It is the responsibility of the respondent to conduct an intellectual property search and take all necessary steps to ensure their proposed project will not infringe or misappropriate any intellectual property right of a third party and/or obtain all necessary consents, assignments and licenses to provide the solution in the project proposal.

### New Intellectual Property

With most projects conducted with ETC:

* All commercialization rights will reside with the collaborator;
* ETC will not assume ownership of any intellectual property (IP) developed by the collaborator or expect royalties from future commercial sales.

# Project Information

## Possible Project Sponsors

|  |
| --- |
| Amgen, AbbVie, Bristol Myers Squibb, Genentech, Merck & Co. |

## Description

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| Biocatalytic synthesis utilizes proteins (enzymes) to catalyze organic chemical transformations. Owing to their high selectivity and specificity, enzymes offer significant advantages for the synthesis of pharmaceuticals. Significant advances in enzyme engineering have expanded the scope and utility of biocatalytic transformations in pharmaceutical synthesis, and biocatalysis increasingly is utilized for commercial pharmaceutical manufacture. The efficient, scalable, protein-product separation remains a key challenge for the successful commercial implementation of biocatalysis. Many biocatalytic processes are performed in conventional chemical reactors using one or more unpurified, recombinantly produced enzymes (which contain both the desired enzyme and residual host cell proteins from the expression host). Existing protein-product separation strategies suffer from numerous challenges including volumetric inefficiency, poor protein rejection, and high product loss (*see Appendix Table 1)*. Most approaches must be developed as fit-for-purpose solutions that are tuned for the specific chemistry, scale, and manufacturing infrastructure. They are often insufficiently robust and challenging to develop due to a lack of appropriate scale-down models. As a result, protein-product separation operations require significant engineering resources to develop, introduce substantial risk and process variability, and can negatively impact process productivity and yield. We are seeking information on scalable solutions that separate product from protein from typical biocatalytic reaction streams (*see Appendix Table 2*) and are capable of operating with the following considerations:* Compatible with aqueous / organic solvent mixtures
* Can tolerate insoluble solids
* Can tolerate enzyme loadings up to 50 wt% relative to starting material.
* Aspirationally, the separation technology results in product with < 1 wt% residual protein and has > 90% product recovery

We are interested in both established technologies and novel approaches which could be adapted to conventional small-molecule manufacturing trains without significant facility modification. Examples of novel or unestablished approaches of interest include, but are not limited to:* Thermomorphic Solvent Systems
* Molecularly Imprinted Polymers
* Chemical or biological additives for selective protein precipitation or solubilization
* Novel adsorbents
* Capture of Product or Protein with micelle or other-self assembling system
* Protein engineering approaches for programmed assembly (e.g., T-or chemical-induced self-assembly)

*Ultimately, we seek approaches that maximize product recovery and purity, and enable efficient, robust application and development from kg to tonne production scales for API synthesis.* **Select References:** *In situ product removal:*1. Freeman, A.; Woodley, J. M.; Lilly, M. D., In situ product removal as a tool for bioprocessing. *Biotechnology (N Y)* **1993,** *11* (9), 1007-12.2. Stark, D.; von Stockar, U., In situ product removal (ISPR) in whole cell biotechnology during the last twenty years. *Adv Biochem Eng Biotechnol* **2003,** *80*, 149-75.3. Lye, G. J.; Woodley, J. M., Application of in situ product-removal techniques to biocatalytic processes. *Trends in Biotechnology* **1999,** *17* (10), 395-402.*Crystallization for Product Removal:* 4. Hulsewede, D.; Meyer, L. E.; von Langermann, J., Application of In Situ Product Crystallization and Related Techniques in Biocatalytic Processes. *Chemistry* **2019,** *25* (19), 4871-4884.*Immobilization:* 5. Boudrant, J.; Woodley, J. M.; Fernandez-Lafuente, R., Parameters necessary to define an immobilized enzyme preparation. *Process Biochemistry* **2020,** *90*, 66-80.6. Cao, L., *Carrier‐bound Immobilized Enzymes: Principles, Application and Design*. Wiley‐VCH: 2005.*Pharmaceutical Applications of Enzymes:*7. Basso, A.; Serban, S., Industrial applications of immobilized enzymes-A review. *Mol Catal* **2019,** *479*, 35-54.8. Adams, J. P.; Brown, M. J. B.; Diaz-Rodriguez, A.; Lloyd, R. C.; Roiban, G. D., Biocatalysis: A Pharma Perspective. *Advanced Synthesis & Catalysis* **2019,** *361* (11), 2421-2432.9. Devine, P. N.; Howard, R. M.; Kumar, R.; Thompson, M. P.; Truppo, M. D.; Turner, N. J., Extending the application of biocatalysis to meet the challenges of drug development. *Nature Reviews Chemistry* **2018,** *2* (12), 409-421.10. Hughes, D. L., Highlights of the Recent Patent Literature─Focus on Biocatalysis Innovation. *Organic Process Research & Development* **2022**.**Appendices****Table 1. Overview of established or emerging protein-product separation strategies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Method** | **Description** | **Example Unit Operations** | **Benefits** | **Challenges** |
| **Precipitation and filtration** | Removal by selective precipitation of protein or product to facilitate filtration or similar removal.Examples: * Direct protein precipitation
* *In situ* product crystallization
* Protein denaturation
 | * Dead-end filtration
* Drum Centrifuge
 | Utilizes common equipment found in SM infrastructure  | * Filtration Robustness
* Product Loss
* Slow filtrations on scaleup
 |
| **Extraction** | Removal of the product by partitioning protein and product into different liquid phases. Examples:* Liquid-liquid extractions
* Organic-Aqueous
* Reactive extraction
* Aqueous Two-Phase
 | * Gravity liquid-liquid separations; centrifugal separators
 | * Utilizes common equipment found in SM infrastructure
* Lab-scale development can be performed by process chemists
 | * Identification of conditions or additives which facilitate -product separation
* Challenging for water-soluble products
* Emulsion formulation
* Slow phase separation
 |
| **Permeation** | Separation of protein and product by size or interfacial properties using a membrane or filterExamples:* Pervaporation/Perstraction
* Dialysis
* Reverse osmosis
 | * TFF
* Hollow Fiber Membrane
* Membrane separator
 | * Improved reaction kinetics by continuous product removal
 | * Volumetric Efficiency
* Membrane Fouling
* Specialized high-pressure pumps and separation units
 |
| **Solid-Supported Separative Techniques**  | Separation of protein and product by exploiting differences in adsorption to solid functionalized supportExamples:* Enzyme Immobilization (before reaction)
* Preparative Chromatography
* Adsorption of product or protein to carrier (may include protein denaturation over filter aid etc.)
 | * Packed Bed Reactor
* Dead-end Filtration
* Filter Dryer
* Chromatography
 | * Can be used to remove or reject specific proteins
* Enables use of packed bed reactor (for flow chemistry)
 | * Development of robust immobilizations
* Immobilization can alter enzyme performance
* Supply Chain
* Product Dilution and retention
* Separations: High PMI
 |

**Table 2. Typical Conditions for Relevant Biocatalytic reactions (Parameter ranges are not restrictive for protein removal).**

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Typical Range** | **Unit** |
| Temperature | 10 – 60 | °C |
| Organic Solvent  | 5-100 | vol% |
| Water Content | 4 - 100 | vol % |
| Enzyme Charge | 5 – 50 | wt% relative to the substrate |
| Substrate Concentration | 10 - 100 | g/L |
| Enzyme  | Crude cellular lysates and higher purity preparations |  |
| pH | 6.5 - 10 | pH |

 |

## Requirements

### Necessary Hardware and Software Requirements

|  |
| --- |
| **A. The ETC envisions that a successful submission will meet the following requirements:**1. Compatible with aqueous reactions and common organic solvents (e.g., 2-Propanol, Toluene, Methyl-THF, Isopropyl acetate, Acetone, Acetonitrile, DMSO)
2. The ability to separate product from protein at enzyme loadings as high at 50 g/L (50 wt% enzyme at 100g/L substrate).
3. Recovery of > 90% of product with less than 1 w/v% residual protein
4. Functions in the presence of insoluble solids.
5. Can be operated in pilot and full-scale manufacturing facilities without extensive facility retrofitting. Any equipment should be modular or fit on to a portable skid.
6. Ability to function over a range of temperatures (4°C to 80 °C)
7. Compatible with safety requirements of manufacturing facilities.
8. Electrical design should be compatible for safe handling of processes with flammable materials.
9. Delivery of a scalable model to enable lab development, scale-up, process characterization and technology transfer.

*Note: Solutions that solutions that are process-based (e.g., additives or techniques) and equipment-based are both welcomed.* **B. Where applicable proposed solutions should meet the following additional requirements**:1. Material of construction compatible with reaction conditions (i.e., common organic reaction solvents and acid/bases)
2. Ability to be cleaned for multi-use facilities.
3. Accommodate on-line temperature monitoring, on-line PAT equipment, and sampling capability for reaction monitoring
4. Complies with requirements to operate within a GMP environment
5. Ability to GMP qualify the equipment based on customer needs

**C. Solutions with software control should meet the following additional requirements:** 1. Ability to monitor, control, and record relevant parameters for reactor operation via user interface software
2. System has the capability to communicate to the user control system over a variety of communication protocols

RFI respondents should provide a work plan, including an estimated timeline with milestones, estimated fixed cost to ETC in US dollars, and a description of potential deliverables. |

### Optional Hardware and Software Requirements

|  |
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| Single-use and perpetual use consumable equipment approaches are acceptable. Though less desirable, separation may be performed in multiple iterations/cycles of separation to increase protein rejection (maintaining <10% product sacrifice) |

### Availability Requirements

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| Commercially available and supported system. |

### Licensing Requirements for Commercialized Product

|  |
| --- |
| n/a  |

# Criteria for Evaluation

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| The ETC will evaluate the responses to this RFI based on the respondent’s ability to:* Provide responses reflecting a 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 commercially viable protein-product separation technology.
* 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 RFI.
* Provide any additional capabilities that may differentiate them from other potential collaborators.

Please note that due to the volume of responses received, ETC only provides general updates related to the status of the review process and will not provide individualized feedback as to why a particular proposal was not selected by ETC. |

# Respondent Profile

*(To be completed by respondent)*

Please provide information to the following:

## Company/Organization Information

|  |  |
| --- | --- |
| 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)*

*We encourage all respondents to review the* [***Enabling Technologies Consortium FAQ***](https://www.etconsortium.org/_files/ugd/d6fa33_6713713d571d490ba451f348126fcc35.pdf)*to aid in the development of your response to the RFI.*

## 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:

|  |  |
| --- | --- |
| 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 | Vendor Comments |
| --- | --- | --- |
| Compatible with aqueous reactions and common organic solvents (e.g., 2-Propanol, Toluene, Methyl-THF, Isopropyl acetate, Acetone, Acetonitrile, DMSO) |  |  |
| The ability to separate product from protein at enzyme loadings as high at 50 g/L (50 wt% enzyme at 100g/L substrate). |  |  |
| Recovery of > 90% of product with less than 1 w/v% residual protein |  |  |
| Functions in the presence of insoluble solids. |  |  |
| Can be operated in pilot and full-scale manufacturing facilities without extensive facility retrofitting. Any equipment should be modular or fit on to a portable skid. |  |  |
| Ability to function over a range of temperatures (4°C to 80 °C) |  |  |
| Compatible with safety requirements of manufacturing facilities.  |  |  |
| Electrical design should be compatible for safe handling of processes with flammable materials. |  |  |
| Delivery of a scalable model to enable lab development, scale-up, process characterization and technology transfer. |  |  |
| **If applicable,** material of construction compatible with reaction conditions (i.e., common organic reaction solvents and acid/bases) |  |  |
| **If applicable,** ability to be cleaned for multi-use facilities |  |  |
| **If applicable,** accommodate on-line temperature monitoring, on-line PAT equipment, and sampling capability for reaction monitoring |  |  |
| **If applicable,** complies with requirements to operate within a GMP environment |  |  |
| **If applicable,** ability to GMP qualify the equipment based on customer needs |  |  |
| **Software Control:** Ability to monitor, control, and record relevant parameters for reactor operation via user interface software |  |  |
| **Software Control:** System has the capability to communicate to the user control system over a variety of communication protocols |  |  |

## Estimated Timeline

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## Estimated Project Cost

The overarching goal of ETC is to help bring innovative technologies to the commercial marketplace in partnership with third parties.  Aligned with that goal, participating ETC members will provide resources in the form of funding and subject matter expertise to support the development of this project.  While ETC will entertain all proposals received, regarding funding from ETC, please consider the following:

* Proposed budgets should be provided as **fixed-costs in US Dollars;**
* When partnering with a commercial vendor, any monetary resources provided by ETC should be viewed as seed funding to supplement the total development costs with the collaborator investing as well; *Please review the* [*FAQ document*](https://www.etconsortium.org/_files/ugd/d6fa33_6713713d571d490ba451f348126fcc35.pdf)*, pages 4 through 6 for details regarding funding amounts.*
* When partnering with an academic or non-profit organization, any monetary contributions requested from ETC should be for the total project costs, inclusive of indirect costs (i.e., proposed costs should be inclusive of any indirect or other hidden costs);
* Include a payment schedule, based upon time from project start and/or milestones.

Please describe below project costs, including not only the total project costs but also costs to be paid by ETC and any costs borne by your organization.

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## Commercialization and Support

The overarching goal of ETC is to help bring innovative technologies to the commercial marketplace in partnership with third parties.  Aligned with that goal ETC looks to collaborate on projects which will result in products that are commercially available and supported in the marketplace.

* With most projects, all commercialization rights will reside with the collaborator;
* ETC will not assume ownership of any intellectual property (IP) developed by the collaborator or expect royalties from future commercial sales.

Please describe your organization’s plans for commercialization and support of this technology following the successful conclusion of this project.  If your organization is not a commercial entity (e.g., academic or non-profit), please describe any plans related to the availability of the technology following the successful conclusion of the project. Note that for projects where there isn’t an expectation of a commercial product or service offering, (e.g., research and development project, services-only project) it is expected that each ETC member participating in this project will be provided a non-exclusive, royalty-free license to the output of the project and any new Project IP developed under this project for commercial purposes.

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