REQUEST FOR INFORMATION:

***User-friendly Population Balance Model with Data Integration for Crystallization Development***

*11-June-2016*

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 solicit interest in collaborating together on a user-friendly population balance modeling (PBM) tool that conveniently utilizes available analytical inputs common to crystallization development. The information collected during the RFI process along with subsequent interviews will be used for evaluation purposes, refinement of the subsequent Request for Proposals (RFP), and selection of respondent(s) who will be invited to submit a proposal to the future “User-friendly Population Balance Model with Data Integration for Crystallization Development ” RFP.

## Disclaimer

The contents and information provided in this RFI are meant to provide general information to parties interested in developing the “User-friendly Population Balance Model with Data Integration for Crystallization Development”. 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
* 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 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:

Alexis Robertson

Project Coordinator

ETC Secretariat

c/o Drinker Biddle & Reath, LLP

1500 K St NW

Washington DC, 20005-1209

(202) 842-8800

info@etconsortium.org

[www.etconsortium.org](http://www.etconsortium.org)

## Anticipated Time Frames for Evaluation and Selection Process

Issue RFI July 11, 2016

Questions on RFI due (via email) July 25, 2016

Responses to RFI due August 8, 2016

Presentation to ETC by respondents August 22-26, 2016

Select Finalists for RFP September 6, 2016

***Please submit your response electronically to the above address. Responses received after August 8, 2016 will not be considered.***

# Project Information

## Possible Project Sponsors

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

## Description

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| Commercial off-the-shelf software using population balance models to design crystallization processes are available from multiple vendors. Although the use of these software is increasing across the pharmaceutical industry, the current offerings are limited by several issues which this project is meant to address:* Importation of data into the models is tedious and cumbersome, requiring large amounts of manual pre-processing (reformatting, etc.) prior to parameter regression.
* Only a subset of the available process data (e.g., FTIR concentration data) is used while corresponding FBRM data is not being used for parameter regression.
* There is a need from time-consuming, manual data manipulations to remove noise, filter, and time-average data to improve model convergence.
* Chord length distributions (CLD), which are routinely collected in real-time, are difficult to transform to particle size distributions (PSD) for use in PBMs.
* Model selection (i.e., identification of the appropriate form of the rate and solubility expressions) and parameter regression is often inefficient due to challenges associated with stiff equations, poor model convergence, and lack of integrated approaches to discriminate between potential models.

This project will be a collaboration between ETC and the selected vendor. Throughout the project, the ETC and vendor will work together to develop the desired platform. The ETC will provide the vendor with a comprehensive list of requirements, access to subject matter experts and target end-users, and funding to support the project. The vendor will supply the resources and expertise necessary to design, prototype, and ultimately produce the PBM modeling platform. Upon completion of this project, it is anticipated that the platform will be realized and made available as a commercialized product offering of the participating vendor.  |

## Population Balance Modeling Platform Requirements

### Necessary Hardware and Software Requirements

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| **Ability to easily import process and analytical data into population balance model:** The development of or modification to existing population balance modelling software is requested that provides an intuitive, user-friendly interface to support the development of crystallization processes. The software should allow for directly importing data from varied sources and “native” data formats or files. Further, the software should accommodate individual data streams continuously collected or taken at discrete time points within an experiment. At a minimum, the program must accommodate the following data types:1. Particle size distributions using laser diffraction
2. Chord length distributions using FBRM
3. Concentration using HPLC, which could be entered manually
4. Absorption spectra/concentration using FTIR which should be able to be imported as raw absorbance spectra and calibrated within the program.

The source and additional meta-data for each data stream should be recorded for traceability. Concentration data using FTIR should be able to be adjusted (offset or scaled) to match the measured or modeled solubility when the system is at equilibrium, with the ability to apply the same correction to the remainder of the concentration data. This ability may help mitigate issues with parameter estimation and model stability. The software should have the ability to remove artifacts (e.g., a fines tail) from the particle size distribution in an automated, user-prescribed manner.The program should offer the ability to visualize data while it is being imported and easily overlay data with model predictions. The software should allow the user to select time spans of interest for parameter estimation and model validation. In addition to the analytical data streams, the software should be able to easily import the processing conditions (e.g., temperature, volume additions, agitation rate, pH) during an experiment. These conditions are typically logged by one of the following control systems (listed in order of priority): 1. iControl by Mettler Toledo (CSV export ability)
2. Atlas by Syrris (CSV file format)
3. Pi data historian by OSISoft
4. Delta V

At a minimum, the ability to directly read an iControl file (or a CSV file generated by iControl) is a requirement. It is expected that the process conditions and analytical data could be collected on different computers with the time of each computer not synchronized. The program must have the ability for the user to appropriately align the time stamps for each data stream. **Improvements to parameter estimation**Crystallization population balance models are constructed from a mechanistic understanding of the underlying phenomena and use regressed model parameters, determined from designed experiments, in order to provide desired model fidelity. The most critical requirement is that the program must be designed with the user experience in mind. Use of the application must be intuitive and integrated within a robust modeling platform to ensure a positive user experience. It should be recognized that the intended users of the platform are not full-time modelers and are mostly process development chemists and engineers.Crystallization phenomena are complex and have been modeled using different approaches to describe the same phenomena (e.g., there are several different and valid models for crystal growth). The specific set of phenomenological models that provide the best representation of the phenomena occurring within a process will vary on a case-by-case basis. Therefore, the application should provide a library of existing models from which the user may choose and allow for the option of incorporating custom models. The end user should be able to quickly screen across these models to determine the set that provides the best representation. Further, the ideal platform would provide solutions to and case-studies accounting for the difficulties encountered in numerical integration (e.g., time-step selection, equation stiffness, etc.), in a manner interpretable by the non-full-time modeler.  Parameter regression is a key step in the use of PBM, and challenges such as failure to achieve model convergence often occur when suboptimal guesses are made for each parameter. Methods to mitigate this bottleneck must be included in this program that either ensure sufficiently accurate initial guesses or explore the relevant parameter space in an automated manner. The application must be able to adjust the weight of data appropriately such that discrete and continuous data streams are given the correct level of importance in parameter regression. In addition, relevant measures of statistical confidence in regressed parameters should be provided, including the ability to cross-validate parameters.**Solubility Modeling**The software must have solubility modeling capability built into the tool that allows curve fitting of experimental solubility data. The software should have the flexibility to fit solubility data to different expressions (exponential, polynomial, etc.) and test the curve fit to determine the most appropriate solubility model. The intent is for the user to input solubility data and have a mechanism for verifying the quality of model fit. |

### Optional Hardware and Software Requirements

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| The features listed in this section are desired and would be considered positively differentiating assets, but they are not requirements.**Data input:**In addition to the data input listed in 2.3.1, it would also be desirable to input and utilize:1. UV for assay/solution composition.
2. Multi-dimensional particle size data from source yet to be defined. Must have the ability to at the least import dimensions from image analysis.
3. Comma-separated value data from arbitrary sources.
4. Various universal file formats under development including those being developed by the Allotrope foundation.

It would also be advantageous to be able to pull concentration data directly from HPLC instruments or from Empower. In addition to the requirement of being able to import native file formats, it would be advantageous for the tool to be able to import a standard PDF file exported from the instrument, specifically for laser diffraction, and read it directly into the application. The application should have the ability to recognize the “native” units from the data file being imported and not require conversion of these units outside of the application.The tool would ideally have a graphical interface that allows the users to graphically select a time domain from the plot of the imported data in order to limit the data regression to a prescribed portion of the experiment. This visualization tool should also be able to aid in the time shift of data coming from different sources which are not inherently synchronized.Model Discrimination/Automated Experimental DesignBeing able to select multiple crystallization models simultaneously and then discriminate which model best predicts the experimental data is desired. Ideally the integration between the model and the online analytical tools and experimental platforms would be two-directional which would create the ability to perform adaptively designed experiments in which the next experimental condition is selected by the tool to provide the best model discrimination or parameter estimation. Full automation of the modeling software with the equipment to execute the next best experiment is a vision, not a requirement. Reporting the next set of experimental conditions to run is an acceptable initial deliverable.**Multi-dimensional population balance models**Ideally the tool would have the ability to support both one-dimensional and multi-dimensional PBM. In order to do this, the tool must be able to utilize multi-dimensional particle size and shape information. The ability to quantify dimensions from microscopy images in order to track particle shape for use in converting between PSD and CLD and/or as an input into multi-dimensional PBM is desired.**Computational fluid dynamics**The ability to account for system hydrodynamics by integrating computational fluid dynamics with the population balance models would add to the versatility/applicability of the model and would thus be considered an asset. It is envisioned that this may be achieved in a compartmentalized model fashion. |

### Availability Requirements

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| The expected output is a commercially available PBM. Expected timing is 12 months to deliver scope outlined in section 2.31, 1.5 years to deliver the model discrimination and automated experimental design, and 2 years to incorporate multi-dimensional PBM and CFD outlined in 2.3.2.  |

### Licensing Requirements for Commercialized Product

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| Commercially available software tool. IP owned by the software vendor and/or equipment vendor. |

# Criteria for Evaluation

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| The ETC will evaluate the responses to this RFI based on the vendor’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 “Easily Accessible Crystallization PBM Utilizing Available Analytical Inputs” project.
* 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.
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# Respondent Profile

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

Provide any additional information about your company/organization you would like to provide to aid in the review of your RFI response.

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# Company/Organization Response to RFI

## Proposal

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## Functional Requirements & Specifications

Based upon your proposed approach to deliver a solution, describe how your proposal will meet the requirements and specifications provided in Section 2.3 above.

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## Estimated Timeline

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## Estimated Project Cost

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