The National Institute for Innovation in Manufacturing Biopharmaceuticals

Interoperable Model Module to Simulate Buffer-Induced pH-Shifts During Chromatography Steps Request for Application

RFA Release Date: May 13, 2025

Submission due Date: July 7, 2025

Target Decision Date: Mid-August 2025

NIIMBL

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1. Executive Summary

The mission of the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) is to accelerate biopharmaceutical manufacturing innovation, support the development of standards that enable more efficient and rapid manufacturing capabilities, and educate and train a world-leading biopharmaceutical manufacturing workforce. NIIMBL is pleased to announce this Request for Application (RFA) to participate in the Big Data Program initiative to Simulate Buffer-Induced pH-Shifts During Chromatography Steps. Questions can be sent to projectcalls@niimbl.org.

Funding Opportunity Title: RFA: Interoperable Model Module to Simulate Buffer-Induced pH-Shifts During Chromatography Steps

Applications must be submitted via the NIIMBL Proposal Submission Hub. Applications received after the deadline (see Table 1), or otherwise non-compliant with the submission requirements, will not be considered.

The RFA concludes with a decision to fund or not fund applications by the NIIMBL Big Data Leadership and Modeling and Simulation Team members. Awarded projects will be expected to complete contracting within 90 days after formal notification of NIIMBL's intent to fund. NIIMBL reserves the right to rescind offers of funding to awardees.

Table 1. Timeline

EVENT	DATE
Submission Due by 5:00 pm ET	July 7, 2025
Application Review Period:	Mid-July to Mid-August 2025
Award Decisions Announced	Mid-August 2025
Estimated Project Start Date	Mid-October 2025

Total Amount to be Awarded:

NIIMBL intends to fund up to 1 project under this RFA, with the selected project eligible to receive funding up to $300,000. Cost share requirements are described in the Submission Requirements section,

2. Project Requirements

Background

The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) is announcing a funding opportunity for development of an interoperable model module to simulate Buffer-induced pH-shifts during chromatography steps. Interoperable, in this context means the different information systems, devices, and applications involved with the models access, exchange, integrate, and cooperatively use data. This funding opportunity is facilitated through the NIIMBL Big Data Program (BD) which consists of subject matter expert representatives of NIIMBL member organizations.

Motivations for the project: Computer models can be used to augment laboratory experiments in Biopharmaceutical process design. Chromatography operations, specifically, involve well-designed and understood interactions between biochemically expressed proteins and synthetic porous particle binding sites. Such interactions often involve ionic attraction and binding through titratable pH-dependent adsorbent ligands and protein pH-dependent amino acids and sites. Wash and elution of bound product protein (and impurities) often involves use of buffers of different pH containing salts to disrupt the ionic interaction – an accompanying phenomenon is often buffer-induced pH shifts owing to the binding or release of protons from adsorbent ligands or bound species which overwhelm the buffering capacity of the solution. To accurately predict chromatography profiles, it is necessary to predict the temporal and spatial pH within the chromatography column and link that prediction with the pH dependent adsorption/desorption prediction. (see technical references 1-7 below for more information).

Objectives of the project: Develop software modules which are interoperable with others within the CADET Chromatography Analysis and Design Toolkit (https://cadet-web.de/simulation/about_us/). The resulting modules would increase accuracy of predictions for all chromatography separations which involve ionic interactions (CEX, AEX, Protein-A, Hydroxyapatite, etc.). The modules would also be applicable to many different wash and elution contexts (buffer, salts, adsorbed species, adsorbent ligand, etc.) through use of libraries of titratable group pK values and other parameters needed for the simulation. It is most desirable that modules use open-source tools which do not require special licenses or cost for their use (Python, etc.)

Specific area of Interest and Expected Outcomes

The goal of this project is to develop software modules for prediction of buffer-induced pH-shifts during chromatography steps which accomplish the following:

- Prediction of pH at different locations within the chromatography column at different times through solution of proton equilibrium equations with appropriate pK constants (references 1-7)
    - Create extensible data-model for system data needed for pH calculations (ex. concentration and pK for all buffer components, resin ligand pK and density,

pK of bound protein product). Interoperably read user-provided contextual data from the data-model to enable pH calculations (8).

- Incorporate pH-dependent binding effects into the Binding models used within CADET via use of the "dependence on external function" capability (https://cadet.github.io/v5.0.3/modelling/binding/index.html),
- Ensure interoperability of the pH prediction modules with the suite of CADET modules needed for different mode chromatography predictions (AEX, CEX, Protein-A, HA, etc)
- Demonstrate the performance of the model system by accurately predicting buffer-induced pH shifts, and resulting protein elution shifts, for a set of demonstration cases provided by the BD Program
    - Computational Efficiency: The software must solve equations within a reasonable timeframe. The efficiency of numerical solution methods should be optimized to minimize the time required to obtain a solution.
    - Numerical Stability: The software must employ stable and reliable numerical methods to ensure that the solutions provided are trustworthy and consistent.

Project Outputs and Deliverables

- The participating team will collaborate closely with NIIMBL at regularly scheduled meetings (twice per month) to share their progress and collect advice from subject matter experts within the BD Program.
- At least 8 weeks prior to the end of the performance period, all software modules developed and accompanying use documentation will be delivered to NIIMBL. The software will then be tested by BD Program members and feedback will be provided to the participating team.
- At the end of the period of performance, a workshop will be organized to facilitate extensive discussions among the participating team, the BD Program members, and NIIMBL staff. The workshop will focus on documenting the best practices for use and limitations of the delivered model module(s).
- By accepting NIIMBL funding, participants agree to make developed software modules, simulation results, and input data available to NIIMBL and the community. User documentation sufficient for facilitating transfer to a qualified modeling user is expected.
- Participants may retain any preexisting software and algorithms as proprietary. However, the freedom for which preexisting dependent software can be published, distributed, and used by BD Program members will be a criterion for the selection of funding.

Project Constraints

- Proposals must be consistent with NIIMBL Bylaws and should be labeled as NIIMBL Confidential.
- Proposals will be accepted with the following constraints:
    - A maximum $300,000 of NIIMBL funding per project

- All project team members must be NIIMBL members before the final award decision date
- A maximum 12-month period of performance

Technical References

1) Soto Pérez, Jessica, and Douglas D. Frey. "Behavior of the inadvertent pH transient formed by a salt gradient in the ion‐exchange chromatography of proteins." Biotechnology progress 21.3 (2005): 902-910.
2) Pabst, Timothy M., and Giorgio Carta. "pH transitions in cation exchange chromatographic columns containing weak acid groups." Journal of Chromatography A 1142.1 (2007): 19-31.
3) Pabst, Timothy M., et al. "Separation of protein charge variants with induced pH gradients using anion exchange chromatographic columns." Biotechnology progress 24.5 (2008): 1096-1106.
4) Pabst, Timothy M., et al. "Protein separations with induced pH gradients using cation-exchange chromatographic columns containing weak acid groups." Journal of Chromatography A 1181.1-2 (2008): 83-94.
5) Bankston, Theresa E., Laura Dattolo, and Giorgio Carta. "pH Transients in hydroxyapatite chromatography columns—experimental evidence and phenomenological modeling." Journal of Chromatography A 1217.14 (2010): 2123-2131.
6) Pabst, Timothy M., Johnny Thai, and Alan K. Hunter. "Evaluation of recent Protein A stationary phase innovations for capture of biotherapeutics." *Journal of Chromatography A* 1554 (2018): 45-60.
7) Hahn, Rainer, et al. "pH and conductivity transients during elution of IgG from protein A columns." *Biotechnology Progress* (2025): e3534.
8) Ferko, Enxhi, et al. "Analysing interoperability in digital twin software architectures for manufacturing." European conference on software architecture. Cham: Springer Nature Switzerland, 2023.

Eligibility Criteria

Membership

Proposers need to be a federal employee or NIIMBL member. Non-NIIMBL organizations should submit a partially executed NIIMBL Membership Agreement by 5:00pm EST two weeks prior to the submission due date July 7, 2025. Information on how to join NIIMBL is available at: https://www.niimbl.org/membership/

Cost Share

Proposers must offer and document their cost share commitment consistent with their Membership tier requirements. Project teams should be aware that the institutional cost share requirements for NIIMBL member organizations vary based on institution type (e.g., industry, academic/non-profit organization) and tier level.

Federal Agency Participation

NIIMBL Solicitations are open to Federal proposers. NIIMBL welcomes and encourages the participation of Federal employees. Federal employees may suggest a project that NIIMBL should undertake as a community, participate on a project team, or lead a project, as appropriate, within the mission and constraints of their agency. Participation in a NIIMBL project must be compatible with agency missions and any constraints related to accepting resources from NIIMBL. In general, NIIMBL will try to accommodate the unique needs of Federal proposers in this process to reduce barriers to participation. Federal employees should review the Guide for Information for Federal Stakeholders.

Human Subjects Activities are not expected and will require prior written approval before work can begin.

Vertebrate Animal Activities are not expected and will require prior written approval before work can begin.

3. Application Instructions

3.1 General Instructions

Submissions

Applications must be submitted via the NIIMBL Proposal Submission Hub and must be received no later than the submission deadline in Table 1. Submissions received after the deadline, or otherwise not compliant with the requirements of this solicitation, will not be considered.

Confidentiality

Teams are expected to mark their submissions as "NIIMBL Confidential," in accordance with the NIIMBL Bylaws, limiting access to NIIMBL members or Federal representatives. The exception is the Proposal Abstract, which will be released to the public if an award is made.

3.2 Application

Applications will be evaluated by the NIIMBL Big Data Leadership and Modeling and Simulation Team members, composed of subject matter experts from member organizations and federal stakeholders.

The application must address and include the following:

1. Application Narrative must be no more than 5 pages.
2. Abstract (200 words max; not counted towards narrative page count)
3. Executive Summary (up to 1 page; not counted towards narrative page)
4. Required Appendices (not counted towards narrative page count)

Required Appendices-

Appendix A	Biosketches 2-pages
Appendix B	N/A
Appendix C	Project Plan – **see template**
Appendix D	Budget & Justification (.xlsx & .docx – **see templates**)
Appendix E	N/A
Appendix F	References
Appendix G	List of Acronyms
Appendix H	Project Partner Organization Identification Form – see templates
Appendix I	N/A

All documents listed above should be included in one .pdf file except for Appendices B, C, and D, which should be uploaded separately in their appropriate file format.

Table 2. Summary of Application submission documents.
Abstract

	Constraints
Application Narrative	Maximum of 5 pages File Type: .pdf only
Required Appendices	No page limits. Adhering to templates provided on the RFA 2025.02 webpage. File Type: consistent with templates

Abstract
The abstract must include the PI, if proposing a team project all co-PI names and organizational information of each partner organization if applicable, and a brief description of the proposal. The abstract will be released to the public if an award is made; therefore, proposers are expected to ensure that it does not contain any confidential or proprietary information.

NOTE: The Abstract should be included in the pdf file of your proposal documents. You will also be required to copy and paste the Abstract into a text field in the Submission Hub. The names and organizations are not included in the 200-word count.

Application Narrative

This section should include a complete and compelling description of who you are, what you intend to do, why you can accomplish the work, and what you will deliver at the end of the performance period. In addition to the following content, include considerations for how the team will communicate, maintain timelines, stay within budget, and how decisions will be made.

- Team - Principal Investigator and any other senior/key personnel that will play a leadership role on the project. Each of these individuals should have a Biosketch (Appendix A).

- Technical Approach – Mathematical means to calculate pH (ex. Pabst_2007_ pH transitions in cation exchange chromatographic columns containing weak acid groups), means of interoperability (ex. “CADET external function link”, Ferko, Enxhi, et al. "Analyzing interoperability…), means of extensibility for user flexibility (ex. buffer pK digital library), Software programming language (ex. Python).
- Description of Team Capabilities - capabilities at your organization that enable the work to be carried out, including personnel, instrumentation, and facilities.
- Description of Outputs – software modules, example computations, user manuals, periodic update presentations, videos of example computation workflows, etc.

3.3 Required Submission Appendices

Appendix A: Biosketches

Provide biosketches for the PI and all named senior/key personnel. Biosketches are limited to two pages each.

Appendix B: Quad Chart

N/A

Appendix C: Project Plan

The project plan should include a Gantt Chart detailing the major tasks, and deliverables for the proposed project. It will visually show how the work will be completed over time, with a minimum of 1-month increments. **The Period of performance is not to exceed 12 months**. The Gantt chart should be submitted as a .pdf, or .xlsx file.

Appendix D: Budget & Justification

The Budget should be broken into requested funding segments that align with the Gnatt Chart in the Project Plan. The budget should include the NIIMBL funding request and cost share commitment and be submitted as an xls. File. The budget justification should be a written narrative explaining in detail the need for the identified cost categories and submitted in a docx. file.

Appendix E: BRL Evaluation

N/A

Appendix F: References

Provide a complete list of references cited in the project proposal. If references are not used, indicate N/A.

Appendix G: List of Acronyms

Provide a complete list of acronyms used in the project proposal. If acronyms are not used, indicate N/A.

Appendix H: Subrecipient Commitment Form

The proposing organization must submit either a Subrecipient Commitment Form or a Letter of Intent.

If your organization is a federal agency or is a participant in the Federal Demonstration Partnership (FDP) Clearinghouse, your organization should submit a Letter of Intent.

All other organizations requesting NIIMBL funding and committing cost share are required to complete and submit the Subrecipient Commitment Form.

Large Industry partners who are only providing a leveraged cost share commitment, volunteer participating organizations essential to complete the project or from an end user of the developed technology, and state cost share commitments should complete a Letter of Commitment.

Templates can be found on the NIIMBL website.

4. Application Review and Evaluation

4.1 NIIMBL Review Process

Applications must comply with the requirements outlined in this RFA. All formatting requirements, administrative requirements, terms and conditions, and other requirements will be assessed for completeness.
Automatic rejection will occur if the submission is received after the published deadline or if the proposer did not meet the deadline to submit a membership request.
NIIMBL will review applications to ensure suitability of the work within the project description (see Section 2 of this RFA). Applications will be provided to the Big Data Program Leadership and Modeling and Simulation Team for review.

4.2 NIIMBL Acceptance Criteria

NIIMBL Subject Matter Expert Review Panel

Proposals will undergo a merit review by a panel of subject-matter experts, and will be assessed using the following criteria:

1. The proposal's ability to address the defined need outlined in the project description (section 2 above)
2. The proposal team's capability to provide a solution
3. Budget requested, funding and cost share commitment

5. Reporting

Project reporting requirements will be outlined in the Subaward contract.

6. Abbreviated List of Acronyms

1. RFA: Request for Application
2. BD: Big Data Program
3. Co-PI: Co-Principal Investigator
4. FDP: Federal Demonstration Partnership
5. IP: Intellectual Property
6. NIIMBL: National Institute for Innovation in Manufacturing Biopharmaceuticals
7. PI: Principal Investigator
8. CADET: Chromatography Analysis and Design Toolkit
9. CEX: Cation exchange chromatography
10. AEX: Anion exchange chromatography