NIMBL

The National Institute for Innovation in Manufacturing Biopharmaceuticals

Project Call 2.1
Request for Proposals

Concept Papers due: JUNE 14, 2018

Proposals due: AUGUST 29, 2018

VERSION May 17, 2018 | AMENDED May 25, 2018

NIMBL

Table of Contents

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 Project Call 2.1 with member-driven and industry-led priority topic areas for technical and workforce development projects.

Funding Opportunity Title: Project Call 2.1

Stages:

Stage 1: Concept Phase

Technical Projects: includes a 4-page concept paper, 3-slide presentation, no teaming or budget information required.

Workforce Projects: includes a 1-page concept paper, 1-slide presentation, no teaming or budget information required.

Phase concludes with presentations to the NIIMBL membership at the Project Call 2.1 Summit, to seek an invite to Stage 2.

Stage 2: Full Proposal Phase includes a 15-page proposal with teaming, detailed budget, cost share, and other requirements listed in this announcement. This Phase concludes with a decision to fund or not fund the proposal by the NIIMBL Governing Committee (GC).

Key Dates:

Tentative dates will be set, based on feedback from the committees, to maximize participation

EVENT	DATE
RFP Release	May 17, 2018
RFP FAQ Webinars	*May 21-25, 2018*
Concept Paper Due	June 14, 2018
Project Call 2.1 Summit	*June 21-27, 2018*
Invite for Full Proposal	*June 29, 2018*
RFP FAQ Webinars	*July 2-6, 2018*
RFP FAQ Webinars	*July 23-27, 2018*
Full Proposal Due	August 29, 2018
Proposal Review	*September 17-21, 2018*
Committee Review	*September 24-28, 2018*
Award Decisions Made	*October 1-5, 2018*

Stage 1: Concept Phase submissions must be submitted by e-mail to projectcalls@niimbl.org marked with "NIIMBL Project Call 2.1 PROJECT CONCEPT" and must be received no later than 5 p.m. Eastern Time **Thursday, June 14, 2018**. Submissions received after the deadline will not be considered.

Stage 2: Full Proposal submissions must be submitted through Box.com where NIIMBL will create a private, secure folder on Box.com that is accessible only to team personnel from organizations invited to submit a full proposal. The files must be marked with "NIIMBL Project Call 2.1 PROJECT PROPOSAL" and must be received no later than 5 p.m. Eastern Time **Wednesday, August 29, 2018**. Submissions received after the deadline will not be considered.

All submissions will be acknowledged by a return email confirmation from NIIMBL.

Funding Opportunity Description:

Further details on project topics are in Section 6.

Technical Projects:

Technical projects are expected in these high priority "industrial need" categories:
(In no particular order)

- Process Analytical Technologies (PAT)
- Rapid release of Drug Substance and Drug Product
- Viral Clearance Technology Development
- Cell Line Development and Engineering
- Manufacturing Platforms for Cell Therapy Products
- Drug Substance Manufacturing - Chromatography Technology Development
- Continuous Processing Technology Development – Biologics
- Scale-down Models for Biologics Manufacturing Process Development
- Mechanistic Model Development
- Cost-Effective Gene Vector Production
- Improved Drug Product Stability
- Novel Materials for Biomanufacturing

Workforce Projects:

Workforce projects requested are short duration. Broad categories are:

- Short Course Development, e.g. technical awareness of biopharmaceuticals designed for executives
- Regional Workforce Assessments, e.g. develop regional workforce needs assessment tools
- Planning Grants plan to develop larger Project Call including e.g. market research

Total Amount to be Awarded: NIIMBL will make available up to $6,500,000; subject to GC approval.

Proposer Eligibility:

Stage 1: Concept Phase, only the lead concept proposer must be an individual from a NIIMBL member organization or a Federal employee.

Stage 2: Full Proposal, a lead project proposer AND the proposed project team must be a NIIMBL member or Federal employee by **Wednesday, August 15, 2018**. Information on how to join NIIMBL is available at www.niimbl.org.

Project Funding Maximums and Cost Share Requirements:

Workforce proposals are a maximum $50,000 of NIIMBL funding and are required to meet a minimum 1:1 (NIIMBL: partners) cost share requirement.

Small technical proposals are a maximum $300,000 of NIIMBL funding and are required to meet a minimum 1:1 (NIIMBL: partners) cost share requirement.

Large technical proposals are a maximum $1,500,000 of NIIMBL funding and are required to meet a minimum of 1:1.25 (NIIMBL: partners) cost share requirement.

The match must be from non-Federal funding sources.

Period of Performance:

Technical proposals must not exceed 18 months.

Workforce proposals must not exceed 6 months.

2. Project Requirements

2.1 Project Types

This project call solicits proposals consistent with NIIMBL Bylaws. Technical project proposals shall be within Manufacturing Readiness Level 4-7. More information on Manufacturing Readiness Level can be found at http://www.dodmrl.com or http://www.niimbl.org/Downloads/Guide_MRLs.pdf.

Proposals may be submitted as Technical or Workforce projects.

2.2 Eligibility Criteria

Membership

To participate on a project proposal team, an organization must be a member or have submitted a partially-executed NIIMBL Membership Agreement by **5:00pm Eastern Time on Wednesday August 15, 2018**. Information on how to join NIIMBL is available at www.niimbl.org.

Cost Share

There is no requirement to have cost share documented or planned at the Concept Phase.

Each project full proposal must offer the required minimum cash or in-kind cost share commitment: a minimum of 1:1 for workforce and small technical proposals and 1:1.25 for large technical proposals. Cost share must be consistent with NIIMBL by-laws and membership agreements.

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. Due to these different cost share obligations, project teams may allocate cost share commitments amongst team members however necessary to meet the minimum overall project cost share. For example, not every team member is required to commit cost share and some team members may exceed the required ratio. However, the project team collectively must still meet the requirement.

Project teams requesting State cost share funding may require additional review and approval from those State organizations to secure their commitment for cost share funding. Project proposal teams with state funding are encouraged to include confirmation of the support (Appendix H). Project proposal teams must contact the appropriate State organization for additional information:

Delaware: Contact Marta Rosario (martar@udel.edu) by 5:00 p.m. on July 30, 2018 to request state cost share. The request should include a 1 paragraph description of the project, partners, and budget narrative.

Massachusetts: Massachusetts applicants should submit a draft application to NIIMBLMA@masslifesciences.com by August 6, 2018. Applicants may need to present their proposal in person to the Massachusetts Life Science Center the week of August 13, 2018.

North Carolina: Contact Jon Horowitz (jmhorowi@ncsu.edu) at the NC State Office of Research and Innovation. Requests need to reach this office by 5:00 p.m. on July 20, 2018.

Teaming

There is no requirement to have any partners identified during the Concept Phase. A goal of the Project Call 2.1 Summit is to help concept proposers connect with Tier 1 industry, small-to-medium enterprise (SME), and other NIIMBL Members to identify partners and cost share opportunities.

Invited Full Proposals must have at least two distinct organizations participating. Each project proposal team shall have a designated lead partner that coordinates the activities of all partners on the project team.

NIIMBL highly encourages inclusion of small-to-medium enterprises. Project teams without a small-to-medium size enterprise must complete a justification form (Appendix I).

Each project proposal must designate a lead organization, Principal Investigator (PI), and a Project Manager.

Note: When appropriate, project proposal teams may seek collaboration with Federal Organizations, National Laboratories, or Federally Funded Research and Development Centers (FFRDCs) within the limits of their mission, rules, and Federal approvals.

Human Subjects Activities

If proposing activities with human subjects, all activities involving human subjects must satisfy the requirements of the Common Rule for the Protection of Human Subjects, as provided for by the Department of Health and Human Services in 45 C.F.R. Part 46 and codified by the Department of Commerce in 15 C.F.R. Part 27. The Common Rule, and the institutional policies that enforce its requirements in activities involving human subjects, exist to ensure adequate protection of human subjects. Additional guidance related to activities involving human subjects is available: http://www.niimbl.org/Downloads/Guide_HumanSubjects.pdf

Vertebrate Animal Activities

If proposing activities with vertebrate animals, all activities must comply with the Laboratory Animal Welfare Act of 1966 (as implemented in 9 C.F.R. Parts 1, 2 and 3), and all other applicable statutes pertaining to the care, handling, and treatment of warm-blooded animals held for research, teaching, or other activities.

3. Proposal Instructions

3.1 General Instructions

Submissions

Stage 1: Concept Phase submissions must be submitted by e-mail to projectcalls@niimbl.org marked with "NIIMBL Project Call 2.1 PROJECT CONCEPT" and must be received no later than **5 p.m. Eastern Time Thursday, June 14, 2018**. Submissions received after the deadline will not be considered.

Stage 2: Full Proposal submissions must be submitted via Box.com, where a NIIMBL will create a private, secure folder that is accessible only to team personnel from organizations requested to submit a full proposal. Submission instructions for the private Box folder will be provided when invited to submit a full proposal. The files must be marked with "NIIMBL Project Call 2.1 PROJECT PROPOSAL" and must be received no later than **5 p.m. Eastern Time Wednesday, August 29, 2018**. Submissions received after the deadline will not be considered.

All submissions will be acknowledged by a return email confirmation from NIIMBL.

Confidentiality

Mark submissions "NIIMBL Confidential" in accordance with the NIIMBL By-Laws and limited to NIIMBL Members or Federal Representatives. The exception is the Full Proposal Abstract, which will be released to the public.

3.2 Stage 1: Concept Phase

The Concept Paper must be single-spaced, 11-point Arial font (or larger equivalent font).

Technical projects require submission of an up to 4-page Concept Paper (not including references) and a 3-slide Concept Presentation.

Workforce projects require submission of a 1-page Concept Paper and a 1-slide Concept Presentation.

The submitter is expected to attend the PC2.1 Summit in person. The submitter will present the concept slides, in a 5-minute timeslot including questions, at a date and location to be determined. The tentative plan is for the Summit to be held around June 21-27, 2018 in the Washington DC Metro region. Note: Though the slides are "NIIMBL Confidential," the presentation will be to an in-person and remote, limited, audience of NIIMBL members and Federal Stakeholders.

Exceptions to in-person attendance may be considered on a case-by-case basis.

The Concept Paper will include:

1. Submitter Name and Contact Information
2. Identified project team partners or desired project team partners and expertise
3. Concept title
4. Project type: Large Technical/Small Technical/Workforce
5. Background of problem to be solved
6. Short description of the proposed concept
7. Short description how this concept solves an industrial need
8. Describe the return on investment resulting from this concept
9. Describe the estimated time to impact on industry
10. Describe how the concept for technology or workforce program to transition to the next phase (i.e. MRL 7 to 8)

Concept Paper template:
http://www.niimbl.org/Downloads/PC2_1_Template_ConceptPaper.docx

NIIMBL intends that Concept Papers do not require Research Office/Sponsored Programs Office (or authorized official) approval for submission. However, individuals should check with their local RO/SPO to comply with institutional requirements.

The Concept Presentation will include:

- Slide 1: Quad Chart (only slide required for workforce projects)
  - Upper Left: Problem and proposed solution, with MRL assessment
  - Upper Right: Current state of the art (what are you replacing?)
  - Lower Left: Submitter name & potential/desired project team
  - Lower Right: Return on investment in the concept
- Slide 2: Visual depiction of concept (graphs, schematics, pictures, workflow maps)
- Slide 3: (Optional) Submitters choice to help the audience better understand the concept such as technology goals, technology needs, partner needs, regulatory considerations, workforce goals, workforce needs, funding concerns, schedule concerns, market development, etc.

Concept Presentation template:
http://www.niimbl.org/Downloads/PC2_1_Template_ConceptPresentation.pptx

Concept papers that are not aligned with the Project Call 2.1 Topics (section 6 of this RFP) will not be invited to give an in-person presentation at The Summit.

3.3 Stage 2: Full Proposal

Technical Projects: The full proposal narrative must be no more than 15 pages.

Workforce Projects: The full proposal narrative must be no more than 5 pages.

The full proposal is NIIMBL confidential except for the abstract which will be released to the public. The full proposal must address and include the following:

1. Proposal Cover sheet(s) (not counted towards the page count)
2. Abstract (less than 1 page; not counted towards the page count)
3. Proposal Narrative (technology projects: 15 pages; workforce projects: 5 pages)
    1. Executive Summary
    2. Background and Significance
    3. Project Description
    4. Potential Project Impact
    5. Description of Team
    6. Project Management Plan

4. Required Proposal Appendices (not counted towards the page count)

Appendix A	Biosketches
Appendix B	Quad Chart
Appendix C	Work Breakdown Structure and Responsibilities Assignment Matrix
Appendix D	Individual Organization Budgets

5. Additional Proposal Appendices (not counted towards the page count)

Appendix E	References
Appendix F	List of Acronyms
Appendix G	Letter(s) of commitment
Appendix H	Small to Medium Enterprise partner exemption request

To assist in the proposal preparation, templates for the proposal can be found at:
http://www.niimbl.org/PC2_1.php

A proposal completion checklist can be found at:
http://www.niimbl.org/Downloads/PC2_1_ProposalChecklist.pdf

Proposal Cover Sheet

Each unique project organization on the project proposal team must submit a Proposal Cover Sheet. All project proposal team organizations must be NIIMBL members or a Federal Entity. [http://www.niimbl.org/Downloads/PC2_1_Template_ProposalCoverSheet.pdf]

Abstract

The abstract includes the names and information of the lead organization, each partner organization, the PI, all co-PIs, and a brief description of the proposal. The brief description is limited to 200 words that will be released to the public; therefore, please ensure that the brief description does not contain any confidential or proprietary information.

Proposal Narrative

The proposal narrative must be single-spaced, 11-point Arial font (or larger equivalent font). The proposal narrative must include all the sections described below and must not exceed 15 pages for technical projects and 5 pages for workforce projects (including the Executive Summary).

1. **Executive Summary** (1-page maximum)

   Summarize the proposed work including the technology or workforce development objectives and how they are consistent with the Project Call Topic and NIIMBL goals, MRL level (for technical projects), and the projected impact of the project.

2. **Background and Significance**

   Identify the project call topic area being addressed and describe the specific problem or current state of the art. Summarize prior work done in the area, preliminary results, and the starting/ending MRLs of the work being proposed.

3. **Project Description**

   The Project Description must include a Gantt chart, aligned to the Work Breakdown Structure (WBS) in Appendix C, to define stages or tasks that contain clear go/no-go decision points or milestones, and deliverables.

   NOTE: Appendix C will cross reference the WBS with the page number in the narrative where additional details can be found. Appendix C will also contain a Responsibility Assignment Matrix that will describe how the responsibilities for the work will be shared. Appendix C does not count towards the total page count.

4. **Potential Project Impact**

   Summarize the impact of the proposed project to the overall goals and objectives of NIIMBL. Describe how this proposal is an improvement over the current state-of-the-art, planned measures of success, regulatory considerations, and significance of this project for the industry.

   For example, technical impact on productivity, quality, efficiency, energy usage, efficacy, potency, safety, and/or any other important factors. Economic impact in this sector such

as the development of a highly trained workforce, scalability of technical or workforce projects, the future of biomanufacturing, and/or estimated economic impact on a company or on the industry broadly, or any other relevant measure. Measurable or quantifiable improvements are strongly encouraged.

5. **Description of Team**

   Identify the Principal Investigator (PI) from the lead organization for the project proposal team, the Co-PIs from partner organizations, other senior/key personnel, and the project proposal team's identified Project Manager. Additional senior/key personnel (those team members who are not identified as the PI or co-PIs) may include staff whose participation and/or leadership is critical for the success of the project. Graduate students, postdoctoral students or laboratory technicians should not be considered senior/key personnel. For all identified team members, include their responsibilities and roles in the project.

6. **Project Management Plan**

   Describe the project management approaches to ensure the synergistic work across project team members, in particular any handoff of work between organizations. Include how the team will ensure timelines, budget and risk will be actively managed and decisions will be made.

A template for the Abstract and Proposal Narrative can be found at:
http://www.niimbl.org/Downloads/PC2_1_Template_ProposalNarrative.docx

Required Proposal Appendices

Appendix A: **Biosketches**

Provide biosketches for the PI, all co-PIs, and Project Manager only. Biosketches are limited to two pages each, and while no format is prescribed, proposers are encouraged to use the NSF format:
https://www.nsf.gov/pubs/policydocs/pappg17_1/pappg_2.jsp#IIC2f]

Appendix B: **Quad Chart**

Complete a quad chart providing an overview of the proposal's methodology and approach, highlights from the work breakdown structure, the impact, team composition, and budget information. The quad chart is limited to one page. The NIIMBL template is available at:
http://www.niimbl.org/Downloads/PC2_1_Template_AppendixB_ProposalQuadChart.pptx

Appendix C: **Work Breakdown Structure and Responsibilities Assignment Matrix**

The work breakdown structure (WBS) for the proposed project forms the foundation of the proposed project plan. Align the WBS with the Responsibility Assignment Matrix to describe how responsibility will be shared across the identified WBS elements. One WBS is required for each project proposal team and must include all proposed work. The WBS

with a Responsibility Assignment Matrix template is available for download at: http://www.niimbl.org/Downloads/PC2_1_Template_AppendixC_WBSandRAM.docx

Appendix D: **Individual Organization Budget**

Provide individual budget workbooks for the lead organization and each of the partner organizations requesting funding and/or committing cost share to the proposed project. Budgets are to be organized by WBS Level 2 Segments. The budget template allows for 5 WBS Level 2 Segments. Any project proposal team with more than 5 WBS Level 2 Segments is asked to email projectcalls@niimbl.org for further direction on how to complete the budget workbook. The budget template is available for download at: http://www.niimbl.org/Downloads/PC2_1_Template_AppendixD_IndividualOrganizationBudget.xlsx

Additional Proposal Appendices

Appendix E: **References**

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

Appendix F: **List of Acronyms**

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

Appendix G: **Commitment Letters**

Include Letters of Commitment from volunteer participating organizations essential to complete the project or from an end user of the developed technology. If commitment Letter(s) are not needed, this appendix is N/A.

Appendix H: **Small to Medium Enterprise partner exemption request**

If a small to medium enterprise (SME) is not a proposed project partner, then a required explanation must have two components: 1. How do you know that there is no SME available for this project? 2. The basis upon which it was determined to be fair and reasonable not to include an SME. If an SME is part of the project team, this appendix is N/A. A template is available for download at: http://www.niimbl.org/Downloads/PC2_1_Template_AppendixH_SMEExemption.docx

4. Proposal Review and Evaluation

4.1 Stage I: Concept Paper Evaluation Criteria

NIIMBL Acceptance Criteria

Concept Papers and Presentations must comply with information requirements outlined in this RFP. Any pages beyond the 4-page limit for technical projects and 1-page for workforce projects, will be removed before distribution to the review panel.

Automatic rejection will occur if the submission is received after the published deadline.

NIIMBL Administrative Criteria

All administrative requirements, terms and conditions, and other appropriate disclosures will be assessed for compliance with this RFP.

Concept Paper Presentation - The Project Call 2.1 Summit

Concept presentations will be made to Tier 1 industry NIIMBL membership and Federal Stakeholders, and other Concept Paper leads. The NIIMBL Tier-1 industry members will evaluate proposed concepts for the purpose of inviting a full proposal submission, with consideration of the total available funding ceiling. The presentation evaluation criteria are:

1. Does the project solve a relevant industrial need?
2. What is the return on proposed project investment?
3. Time to impact in industry
4. Ability or ease with which to transition a technology prototype or workforce program

Additionally, the presentation provides an opportunity to find teaming partners if the concept is invited to the full proposal stage.

Concept Presentation waiver: A project proposal team leader may elect to waive the presentation step if a concept paper has one or more Tier 1 industry endorsement and a full team of partners. Such requests will be considered on a case-by-case basis.

4.2 Stage II: Full Proposal Evaluation Criteria

NIIMBL Acceptance Criteria

Proposals must comply with information requirements outlined in this RFP.

Automatic rejection will occur if 1) the submission is received after the published deadline, 2) the project team includes only a single organization, and 3) budget parameters are not met, such as the maximum project budget and cost share ratio.

NIIMBL Administrative Criteria

Proposals will be assessed to ensure the budget is appropriate and reasonable for proposed work. All administrative requirements, terms and conditions, and other appropriate disclosures will be assessed.

NIIMBL Subject Matter Expert Criteria

Technical and Workforce proposals will undergo a merit review, and will be assessed using the following criteria:

Strategic Fit & Impact – 40%

a. Does the project solve a relevant industrial need?
b. What is the return on proposed project investment?
c. Time to impact in industry

d. Ability or ease with which to transition a technology prototype or workforce program (i.e. MRL 7 to 8)

Technical Assessment – 60%

e. Technical Approach to solve the problem
f. Ability to solve the problem in the proposed time frame
g. Alignment of cost with project scope
h. Team Expertise to execute the proposed approach
i. Project management plan
j. Generalizability to a broader field of use/sustainability of workforce program

NIIMBL Technical Activities/Workforce Activities/Governing Committee Criteria

Proposals will undergo a NIIMBL membership impact review based on the administrative and technical/workforce reviews. The following criteria will be used:

1. Strategic benefit to NIIMBL members
2. Industry interest
3. Small to medium size enterprise involvement
4. Contribution to NIIMBL sustainability
5. Alignment of costs with project scope and potential benefits
6. Cost share commitment

In addition, the Governing Committee will take into account total Project Call 2.1 funding available.

5. Reporting

Project reporting requirements will be outlined in the Project Award Agreement and will include

1. Administrative
    a. Monthly invoices to include cash or cost share
2. Technical
    a. Monthly project update and team teleconferences
    b. Quarterly report
    c. Final report
    d. Annual presentation to NIIMBL membership
    e. Post-Award Impact Reporting

6. Project Call 2.1 Topics

Project Call 2.1 topics areas were developed and prioritized by the Technology Activities Committee and the Workforce Activities Committee and approved through the Governing Committee.

To the extent that collaboration with Federal Organizations, National Laboratories, or Federally Funded Research and Development Centers (FFRDCs) is appropriate for the success of a proposed project, consider options to include these individuals or organizations.

6.1 Technology Priority Project Topics

The Project Topic Areas described below were chosen through a series of polls of NIIMBL Technical Activities Committee (TAC) representatives, and a recent series of individual discussions with technology leaders from Tier 1 industry members. These descriptions are not arranged by of order importance, but they all have been described as industry priorities by at least one Tier 1 company. (Red text signifies amend text after the May 17, 2018 posting.)

Many of these Project Topic Areas have long-term goals that could take multiple years to achieve. Strategically, in Project Call 2.1, NIIMBL is seeking technical proposals from NIIMBL member teams that will make significant progress towards reaching these long-term goals in time periods of 12-18 months. The most attractive projects for funding will offer a combination of the best alignment with industry objectives, and the best promise of making significant progress towards these long-term goals in the shortest time. This is the best way to guarantee that the results of NIIMBL technical projects will provide the best return of investment to industry members, both in the short- and long-term. Examples for each technology topic can be found at:
http://www.niimbl.org/Downloads/PC2_1_Supplement_TechnicalTopicAreaExamples.pdf

6.1. Process Analytical Technologies (PAT)

Develop novel process analytical technologies (PAT) that provide manufacturers of both biologics and cell and gene therapies with in-line, on-line, or at-line measurements of important process parameters, critical quality attributes and process and product impurities. Sensors that can be applied to speed up current processes and enable future intensified (connected) or continuous processes are of interest to manufacturers. Development of at-line or ideally in-line tools to monitor key cellular and/or product attributes for the purpose of more rationally feeding cell culture processes to increase productivity and tighten control of key product attributes. These sensors could be used with *in-silico*/AI models of cellular metabolomics that can be developed based on large experimental datasets to develop control schemes. Single-use, robust sensors that do not require calibration are needed in both drug substance and drug product applications, especially for single-use UV measurements, pH, temperature, dissolved oxygen, CO_2, and a wider variety of analytes and process parameters that can operate on a wider range of conditions. In-line monitoring combined with multivariate analysis (MVA) will enable feedback/feedforward methods to control critical quality attributes of the product. Microfluidic electrophoretic chips, near infrared (NIR) spectroscopy, Raman spectroscopy and mass spectrometry-based methods are among the technologies that would be of interest to apply to in-line, on-line or at-line sensors. Of particular interest are PAT projects in process platforms related to flexible manufacturing of biologics that have a regulatory science aspect to mitigate risks in using pooled Critical Quality Attributes (CQA) data and Quality by Design (QbD) knowledge from member companies. Also of interest are inferential methods or "soft sensors" to predict product quality attributes in real time, contact-free in-line PAT and product potency assays, and novel analytical and data technologies that can be used on the floor to detect lot-to-lot raw material variability.

6.2. Rapid Release of Drug Substance and Drug Product

Analytical testing currently causes significant delays due to the time it takes to complete the complex and comprehensive characterization needed to ensure raw material quality as well as product identity, purity, and potency. Current compendial methods used for adventitious agents (AA) are time-consuming, with culture-based testing taking up to 28 days. Industry needs include faster detection of microbial, mycoplasma, and/or viral contaminants, and faster and more sensitive methods for endotoxin detection. These could be applied to final product testing or testing in-process, with an overall goal to have results available within 24-48 hours. New approaches could involve molecular methods (e.g. NGS, qPCR) for detecting viral nucleic acids. On-line virus detection would be particularly attractive. The focus should be on validation of AA testing methods and providing a framework for getting acceptance from regulators. Highly robust systems for small-volume, non-invasive automatic, sub-visible particle detection and sizing/characterization are needed to reduce the number of false rejects. Projects that include regulatory science in determining potential issues during implementation of these rapid AA technologies are particularly welcome.

6.3. Viral Clearance Technology Development

There is an unmet need for new unit operations for clearance of viral contaminants. Downstream viral clearance operations are critically important for ensuring adventitious agent control in biomanufacturing of protein and mAb therapeutics. These unit operations may not be compatible with continuous manufacturing operations. Virus validation strategies for connected/integrated processes are needed. Particular interest should be placed on projects that involve novel viral clearance approaches using platform processes. There is also a need for standardized, purified, high titer virus challenges that can help establish the required 5 log reduction values for virus removal, and regulatory science to establish protocols for measurement and characterization.

6.4. Cell Line Development and Engineering

Develop novel cell lines that have increased productivity and/or increased manufacturability to decrease cost of goods for protein and mAb biotherapeutic products. The CHO cell line is the workhorse of the protein and mAb manufacturing industry, where post-translational modifications are important for ensuring safety and efficacy of the product in humans. Use of CHO imposes limitations, however, due to the slow growth rate and shear sensitivity. Manufacturers require ultra-high throughput clone selection methods to evaluate tens of thousands of clones to determine the best candidates with high productivity, stability and other desirable features. New cell lines, either CHO or other, would enable manufacturers to increase titers or reduce production times in existing processes or to utilize processes and/or equipment that are not currently compatible with mammalian cell cultures. One potential approach is to consider the development of novel host cells that have higher titer, higher cell density, and improved glycosylation profiles while providing reduction in virus-like particles and host cell proteins. There is also interest in novel approaches to monitor the metabolism of the cell culture through the gas phase composition or through characterization of individual cells in the bioreactor, and for media/feed optimization approaches for intensified or continuous CHO cell culture. *In-silico* or AI modeling of cellular metabolomics, based on large experimental datasets, would enable development of at-line or in-line tools to monitor key cellular and/or product attributes for the purpose of feeding cell culture processes to increase productivity and tighten control of key product attributes.

6.5. Manufacturing Platforms for Cell Therapy Products

Manufacturers are interested in the development of both custom bioreactors as well as scale-down models for allogeneic operation. Rather than rely on existing platforms for cell growth, it is important to design scaffolds and bioreactors that meet the specific needs of cell therapy manufacturers and facilitate in-process measurements and process control. There is great interest in microfluidic manufacturing platforms for culturing T-cells at volumes less than 1 mL with pH, and temperature control. Ideally, these microfluidic chips will have ports to take samples, measure metabolites and deliver complex combinations of ligands and growth factors in a cost-efficient manner. They also should be designed to allow imaging of the cells during the growth process. Manufacturers are also interested in automated RNA and DNA extraction devices for online nucleic acid measurements of cultured cells in a bioreactor. Custom bioreactors for T-cell manipulations (selection, activation, transduction) with low shear stress, high mass transfer capability and integrated on-line, in-line sensors for measuring metabolites are needed. Alternative, low cost reagents for growth factors, cytokines along with novel growth factor delivery modalities with extended release are of interest for cell therapy manufacturing processes. It is of interest to identify and chemically synthesize small, inexpensive molecules such as peptides that can bind to T cell receptors and elicit signals similar to those of growth factors that are made using recombinant methods and are therefore more expensive. There is also interest in solid phase growth factor delivery vehicles in bioreactors that can provide more control and longer exposure to cells and can drive down cost of goods.

6.6. Drug Substance Manufacturing - Chromatography Technology Development

There is an interest in product capture technologies for downstream recovery of protein biotherapeutic products that are single-use, low cost, can handle very high titers, and are amenable to integration into continuous manufacturing operations. High-throughput, high-capacity membranes that can operate at very short residence times because of low diffusional limitations can exhibit higher productivity than chromatographic columns. Manufacturers require novel separation methods (chemistries, resins, ligands) for the selective flow-through removal of antibody fragments and other product impurities (aggregates, charged variants) beyond HCP. Novel and robust resin cleaning and sterilization agents and technologies are needed to extend chromatography media lifetime. Clean, standardized high titer virus preparations are needed to enable higher log reduction value (LRV) claims**.** Projects in this area would also benefit from collaborations with regulatory scientists on measurements and approaches that would facilitate validation and batch release using these technologies.

6.7. Continuous Processing Technology Development – Biologics

High volume biopharmaceuticals made in very large batches to handle the needs for large dosages and/or large patient populations are potential candidates for conversion from single-batch processes to continuous or connected processes. Test bed platforms are needed as a “safe place” to analyze modular, connected, or fully continuous manufacturing of biologics. These test beds would be used for training, introducing novel on-line or in-line sensors for process measurement and control, and testing new equipment for continuous or semi-continuous manufacturing. In addition, these platform processes could be used for risk

assessment. Examples include testing concepts for adventitious agent removal and monitoring, achieving specific residence time distributions and holds, and demonstrating regulatory approaches to batch validation. Continuous or semi-continuous processes will rely greatly on process modeling, control and automation for proper operation. These test beds would offer an ideal environment for the development of such systems. This effort would be greatly enhanced with a regulatory science perspective on process monitoring and CQA measurements to facilitate and de-risk process validation and batch release. In addition to test beds, manufacturers need novel in-line methods to determine the metabolic state of cells in a continuous or semi-continuous process and strategies for optimizing media/nutrient feed protocols specifically designed for these operations.

6.8. Scale-down Models for Biologics Manufacturing Process Development

Develop improved scale-down models for the entire biologics platform process (bioreactor, chromatography, filtration, drug product formulation) to enable more rapid and cost-effective process development. Biopharmaceutical manufacturers rely on scale-down models of the manufacturing process as a risk mitigation strategy to determine the impact of operating variables on process performance and product quality. Automated, improved scale-down models with high-throughput testing capability and predictive modeling for the entire process are required. The modeling efforts could also result in improved scale-up protocols for manufacturing. The scaled down models would include all features that are important in the full-scale reactor, including mass transfer, shear effects, temperature, heat transfer, and agitation. Even though there are commercially available automated scale-down models for bioreactors that can be used for testing media and other process conditions, there are difficulties in scaling these to pilot plant or production levels. There are high throughput screening approaches for chromatography but they also are not fully scalable. Less common are scale-down approaches for high-throughput screening of filtration or product formulation processes. Development of these scale-down devices needs to be accompanied by multivariate analysis (MVA) driven models or mechanistic models of these devices to make them suitable for industrial use. There is also interest on semi-continuous or continuous lyophilization prototyping and development using sensitive analytics for fast process optimization and scale down or modular prototypes for semi-continuous downstream processes, including countercurrent tangential flow chromatography. The data obtained from the scale-down models would be extremely useful in developing mechanistic models.

6.9. Mechanistic Model Development

Develop mechanistic models for biomanufacturing unit operations. First principles, mechanistic models of bioprocess unit operations allow manufacturers to define the appropriate design space and operating ranges for their processes, in contrast to factorial design models. Modeling of unit operations for design of new processes (e.g. continuous/semi-continuous) is one key application. This includes models of mixed-mode chromatography and overload/elution chromatography that can be used for future feedback control of manufacturing steps. Another alternative would include adaptive process control based on in-situ metabolite or product attribute measurements that can help control metabolism, glycosylation and other features of the process. Such mechanistic models can also guide scale-down high-throughput approaches to accelerate screening of operating variables, as well as scale-up efforts from the laboratory to

pilot scale and beyond. There is a need for *in-silico* evaluation methods for new downstream process designs with built in benefit/cost ratio analysis and comparison to current processes.

6.10. Cost-Effective Gene Vector Production

The production of gene therapy vectors is often one most expensive manufacturing steps for clinical trials and commercial-grade gene and cell therapy products. In addition, vector production is often carried out at a contract manufacturing organization, and due to capacity constraints, the wait for supply of gene vector can be rate-limiting for clinical trial activities. Manufacturers would be interested in novel cost-effective alternative processes for production of clinical grade gene vectors, especially those that would enable increased flexibility at the site of vector production. These new processes would utilize novel membranes, filters, resins and other approaches specifically designed for gene vector production. In particular flow-through approaches that take advantage of the relatively large size of gene vectors compared to proteins have high potential for removal of HCP and other impurities.

6.11. Improved Drug Product Stability

It is important to develop novel approaches to improving the stability of drug products to extend shelf life and potentially to eliminate cold-chain supply issues. This can be done via the use of molecular modeling to influence drug design and address drug stability issues, and improved technologies for drying or lyophilization. These computational and experimental tools could inform molecular design to reduce aggregation and immunogenicity of drug product. It is also important to understand excipient interactions with biologics and their impact on the properties of a formulation, including shelf life, solution phase behavior and stability. Manufacturers need approaches for correlating microscopic or molecular properties with solution phase behavior and product stability during drying and storage.

6.12. Novel Materials for Biomanufacturing

There is a need for improved materials for biomanufacturing devices that have acceptable levels of leachables, extractables and particulates, and the ability to withstand low and high temperatures during transport and storage. The industry needs films with better extractable profiles for storage and transport of cryopreserved drug substance (50-100 mL bags). Novel materials with low thermal expansion coefficients and low leachables/extractables profiles are needed for cryopreservation of cell therapy products in syringes. Alternative drug product containers such as IV bags that can withstand low and high temperatures, exhibit low to no particulates, leachables/extractables are of interest to manufacturers. There is a need for silicone-free container-closure components and devices (e.g. high-volume pumps and syringes). In addition, there is a need for single-use devices such as bioreactors that exhibit high mass transfer rates to support high cell density cultures. High cell density cultures also offer significant challenges in cell retention in perfusion bioreactors and in cell harvesting. New single-use devices using materials that can be applied to both issues would be of interest.

6.2 Workforce Development Topic Areas

Workforce Project Topics are suggested based on existing NIIMBL workforce projects and aimed to further develop a NIIMBL community-wide workforce development plan.

Short Course Development

Development of short, online, and readily sharable curriculum modules or short courses e.g. biopharmaceutical manufacturing basics for executives and regulatory officials.

Regional Workforce Assessment

Implementation of NIIMBL workforce assessment tools regionally.

Planning Grants

Establish and convene partners, conduct needs/market research, and develop robust project plan for Project Call 2.2. Examples of the following strategies include:

- Strategies to promote dissemination and sharing of curriculum
- Internship and Apprenticeship programs
- Professional skills development programs e.g. case competitions
- Augmented reality, virtual reality, or other digital learning solutions for training
- Biopharmaceutical training for veterans