The National Institute for Innovation in Manufacturing Biopharmaceuticals

Project Call 4.1T
Request for Proposals

Concept Papers due: October 22, 2020

Full Proposals due: February 4, 2021

VERSION October 1, 2020

NIMBL

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NIIMBL

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 4.1 with member-driven and industry-led priority topic areas for technical, workforce development, and global health projects. This document contains information for technical projects. For information on workforce projects, please reference Project Call 4.1W. For information on Global Health Fund (GHF) projects, please reference Project Call 4.1G.

Funding Opportunity Title: Project Call 4.1T (Technical)

Stage 1: The Concept Phase includes the submission of a Concept Paper that is limited to 4 pages (not including references) and a short slide deck (see details below). No teaming, detailed budget, or cost share information is required at this stage. Concept Phase submissions must be submitted via the NIIMBL Proposal Submission Hub. All submissions must be received no later than 5:00 p.m. Eastern Time **Thursday, October 22, 2020**. Submissions received after the deadline, or that are not compliant with the page / slide limits, will not be considered.

Following submission of Concepts, each will be reviewed by industry subject matter experts to prioritize those Concepts that have the potential for the highest industry impact and likelihood of success. Factors for invitation to full proposals include the feedback from industry, alignment with prioritized areas noted in this RFP (see below), and the readiness level of a given Concept. The Concept Phase (Stage 1) concludes with invitations or declinations issued for submission of a Full Proposal in Stage 2 of the process.

Stage 2: The Full Proposal Phase includes submission of a 14-page proposal with teaming, detailed budget, cost share, and other requirements listed in this announcement. Full Proposal submissions must be submitted via the NIIMBL Proposal Submission Hub. Proposals must be received no later than 5:00 p.m. Eastern Time **Thursday, February 4, 2021**. Submissions received after the deadline, or otherwise non-compliant with the submission requirements (see below), will not be considered.

The Full Proposal Phase concludes with a decision to fund or not fund the proposal by the NIIMBL Governing Committee (GC).

EVENT	DATE
RFP Release	October 1, 2020
Concept Paper Due	October 22, 2020
Invite for Full Proposal	Expected by December 1, 2020
Full Proposal Due	February 4, 2021
Proposal Review	February - March 2021
Award Decisions Made	Expected end of March 2021

Priority Topic Areas

Technical projects are expected in these high priority industrial-need categories *(in no particular order)*

1. Analytical technologies for vector manufacturing
2. Cell processing technologies and analytical technologies for live cell products (cell therapies)
3. Technologies for intensified processing of therapeutic proteins

Opportunity Description: Further details on project topics are found in Section 6.

Total Amount to be Awarded

NIIMBL will make available up to $2,800,000 to fund proposals submitted in response to a combination of the PC4.1T and PC4.1W request for proposals, subject to GC approval.

2. Project Requirements and Eligibility Criteria

Project Types

Proposals must be consistent with NIIMBL Bylaws. Technical project proposals shall be within NIIMBL Biomanufacturing Readiness Level (BRL) 4-7. More information on BRL can be found at http://www.niimbl.org/project-call-4-1.

For Project Call 4.1T, Full Proposals are accepted with the following parameters:

- A maximum $350,000 of NIIMBL funding
- A minimum 1:1 (partners: NIIMBL) cost share requirement
    - All committed cost share must be from non-Federal funding sources.
    - Higher cost share ratio (partners:NIIMBL) will be considered favorably in the review
- A maximum of 18-month period of performance

This project call solicits proposals for Institute-Wide Projects; however, projects may request to be treated as Partner-Specific Projects[1]. License rights to intellectual property developed in Institute-Wide Projects and Partner-Specific Projects are treated differently; therefore, project teams should carefully review Article IV of the NIIMBL Bylaws before requesting that

[1] Institute-wide Projects address broad challenges faced by the biomanufacturing industry at large, with the goal of developing solutions that will benefit the overwhelming majority of manufacturers. Partner-specific Projects address the needs of more narrow sectors of the biopharmaceutical industry and are more limited in participation and IP than Institute-Wide Projects, performed pursuant to a Project Award Agreement. See Article IV of the NIIMBL Bylaws for more information related to intellectual property rights.

a project be authorized as Partner-Specific. NIIMBL envisions occasions where Partner-Specific projects are applicable to the technology being advanced will be extremely rare. If Project teams plan to request permission to be treated as Partner-Specific, they must make this request in the Proposal Narrative and provide a justification for the request. Such a designation will be reviewed prior to project authorization to ensure it is appropriate for the type of project being proposed. Approval for a project to be designated as Partner-Specific is subject to the special approval of the Governing Committee, which will review the justification closely to determine if a Partner-Specific designation is in line with the intent of the distinction.

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 Phase, the lead project proposer AND all members of the proposed project team must be a NIIMBL member or a Federal employee. To participate on a project proposal team as a NIIMBL member, an organization must be a member or have submitted a partially-executed NIIMBL Membership Agreement by **5:00 p.m Eastern Time on Thursday, January 28, 2021.** Information on how to join NIIMBL is available at niimbl membership-information.

Cost Share

There is no requirement to have cost share documented or planned at the Concept Phase. However, Full Proposals must offer and document the required minimum cash or in-kind cost share commitment in the budget that is submitted as part of the Full Proposal. Cost share must be consistent with NIIMBL Bylaws 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 ratio required by their Membership Agreement. However, the project team collectively must still meet the requirement and each project team member must individually meet their requirements per their Membership Agreement, as applicable.

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 I). Project proposal teams must contact the appropriate State organization for additional information:

Delaware: Contact Marta Rosario (martar.udel.edu) by 5:00 p.m. Eastern Time on January 15, 2021 to request state cost share. The request should include a 1-paragraph description of the project, partners, and budget narrative.

Massachusetts: Massachusetts applicants planning to submit a full proposal and requesting cost-share from the Massachusetts Life Sciences Center should reach out to NIIMBLMA@masslifesciences.com early in the application process to confirm requirements and dates. MA applicants will be required to submit a draft application to NIIMBLMA@masslifesciences.com the week of January 4, 2021. Selected applicants will present their proposal in person to the Massachusetts Life Science Center mid-January 2021.

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. Eastern Time on December 15, 2020.

Teaming

There is no requirement to have partners identified during the Concept Phase, but if partners have been identified they should be noted in the Concept Paper.

Full Proposals must have at least two distinct member organizations participating on the project. Each project proposal team shall have a designated lead partner that coordinates the activities of all partners on the project team. Teams that are led by industry members are strongly encouraged.

NIIMBL highly encourages inclusion of Tier 3 industry members. Project teams without one or more Tier 3 industry members must complete a justification form (Appendix H).

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. In accordance with regulations, Federal entities are not permitted to commit cost share towards NIIMBL projects to meet the team obligation.

Federal Agency Participation

NIIMBL Project Calls are open to Federal proposers. NIIMBL welcomes and encourages the participation of Federal employees in the project call process, both during the Concept Phase and the Full Proposal Phase. 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 this Project Call process and any resulting projects 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 PC4.1 Guide Information for Federal Stakeholders available at: http://www.niimbl.org/project-call-4-1 and contact NIIMBL's

Federal Technical Program Manager, Kelley Rogers (Kelley.Rogers@nist.gov), with questions regarding Federal participation.

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 at: http://www.niimbl.org/project-call-4-1.

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. Additional guidance related to activities involving vertebrate animals is available at: http://www.niimbl.org/project-call-4-1.

3. Proposal Instructions

3.1 General Instructions

Submissions

Stage 1: Concept submissions must be submitted via the NIIMBL Proposal Submission Hub. All submissions must be received no later than 5:00 p.m. Eastern Time **Thursday, October 22, 2020**. Submissions received after the deadline, or otherwise not compliant with the requirements for a compliant Concept submission, will not be considered (see below for full requirements).

Stage 2: Full Proposal submissions must be submitted via the NIIMBL Proposal Submission Hub. Proposals must be received no later than 5:00 p.m. Eastern Time **Thursday, February 4, 2021**. Submissions received after the deadline, or otherwise not compliant with the requirements for a compliant proposal, will not be considered (see below for full requirements).

Confidentiality

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

3.2 Stage 1: Concept Phase

The Concept Phase is designed to give proposers the opportunity to propose their project ideas for consideration by reviewers comprised of industry representatives and Federal stakeholders. Proposers will provide their concepts in the form of a written Concept Paper, a short Concept Slide Deck, and an Appendix addressing the NIIMBL Biomanufacturing Readiness Level (BRL) for the Concept. Following this submission, NIIMBL will facilitate review of the Concept Papers and Concept Slide Decks by subject matter experts from industry members and federal stakeholders. The feedback from those reviews will identify the Concepts that are best aligned with industry needs and priorities and will inform the selection of invitations to submit a full proposal in Stage 2 of the process.

To be considered during the Concept Phase, proposers must submit their Concept Paper; which must be single-spaced, 1-inch margins, 11-point Arial font (or larger equivalent font) and a maximum of 4 pages (not including references); along with a short PowerPoint slide deck (maximum 5 slides) that adheres to the template provided for PC4.1T at http://www.niimbl.org/project-call-4-1. The Concept Slide Deck may not include recorded voiceover. The Concept Paper, Concept Slide Deck, and Concept BRL Appendix must be submitted via the NIIMBL Proposal Submission Hub by 5:00 pm Eastern Time **Thursday, October 22, 2020**. Submitted concepts that do not adhere to the formatting and length limits for both the Concept Paper and the Concept Slide Deck will be considered non-compliant and will not be considered for further review. There is no page limit for the Concept BRL Appendix.

The Concept Paper must include:

- Submitter name and organization
- Concept title
- Topic area to be addressed
- Identified project team partners or desired project team partners and expertise (if known)
- Background and significance of the problem to be solved
- Current state of the art; short summary of existing solutions to solve the problem
- Description of the proposed concept
- BRL of the proposed concept and short justification; this should be addressed in the Concept Paper and Slide Deck, and also must be addressed via the submission of the Concept BRL Appendix (see template at http://www.niimbl.org/project-call-4-1 for Concept stage)
- Value proposition to project partners, NIIMBL, the NIIMBL community, and/or the United States biopharmaceutical manufacturing industry. Considerations include return on investment, time to impact in the industry, and planned BRL transition

Submission	Constraints

Concept Paper	October 22, 2020, via NIIMBL Proposal Submission Hub	Single-spaced 1-inch margins 11-point Arial font (or equivalent) Maximum of 4 pages File Type: .pdf only
Concept Slides	October 22, 2020, via NIIMBL Proposal Submission Hub	Maximum of 5 slides, adhering to template provided (http://www.niimbl.org/project-call-4-1). Standard size (4:3) File Type: .ppt or .pptx only
Concept BRL Appendix	October 22, 2020, via NIIMBL Proposal Submission Hub	No page limits adhering to template provided (http://www.niimbl.org/project-call-4-1) File Type: .doc or .docx

3.3 Stage 2: Full Proposal

The full proposal narrative must be no more than 14 pages. The full proposal is NIIMBL confidential except for the abstract, which will be released to the public if an award is made. The full proposal must address and include the following:

1. Project Partner Information Form(s), or Letter(s) of Intent (not counted towards the page count)
2. Abstract (200 words max; not counted towards the page count)
3. Executive Summary (up to 1 page; not counted towards the page count)
4. Proposal Narrative (up to 14 pages)
5. Required Proposal Appendices (not counted towards the page count)

Appendix A	Biosketches
Appendix B	Quad Chart (.ppt or .pptx file – see template)
Appendix C	Project Plan (includes Work Breakdown Structure, Responsibilities Assignment Matrix, and Gantt Chart) (.doc file – see template)
Appendix D	Individual Organization Budgets (.xls file – see template)
Appendix E	BRL Questionnaire (.doc file – see template)

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

Appendix F	References
Appendix G	List of Acronyms
Appendix H	Tier 3 industry member partner exemption request
Appendix I	Letter(s) of commitment

All documents listed above should be included in one .pdf file with the exception of Appendices B, C, D, and E, which should be uploaded separately in their appropriate file format. A proposal completion checklist can be found at: http://www.niimbl.org/project-call-4-1.

Project Partner Information Form(s)

Each unique project organization on the project proposal team must submit either a Project Partner Information 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 Project Partner Information Form. Industry partners who are only providing a leveraged cost share commitment should complete a Letter of Commitment (see Appendix I). All project proposal team organizations must be NIIMBL members or a Federal entity. Templates for the Project Partner Information Form and the Letter of Intent are available at: http://www.niimbl.org/project-call-4-1.

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. This description is limited to 200 words. It will be released to the public if an award is made; therefore, teams are expected to ensure that it does not contain any confidential or proprietary information.

NOTE: The Abstract should be included in the pdf 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.

Executive Summary

Summarize the proposed work including the technology development objectives and how they are consistent with the Project Call topic area and NIIMBL goals, initial and anticipated final BRL level, and the projected impact of the project. The Executive Summary is limited to one page, single-spaced, minimum 1-inch margins, 11-point Arial font (or larger equivalent font).

Proposal Narrative

The proposal narrative must be single-spaced, minimum 1-inch margins, 11-point Arial font (or larger equivalent font). The proposal narrative must include all the sections (1 to 4) described below and must not exceed 14 pages (not including references, which is Appendix F).

1. **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 BRLs of the work being proposed. Describe how this proposal is an improvement over the existing solutions or state-of-the-art and how the proposed project will uniquely contribute to solving the above-mentioned problem.

2. Project Description

Describe the project segments, tasks, deliverables, milestones, and go/no-go decision points. Describe the success criteria for the project, including metrics for measuring project success. Deliverables must be specific and quantitative whenever possible.

NOTE: Appendix C will cross reference the Work Breakdown Structure (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 and a Gantt Chart that will show how the work will be performed over time. Appendix C does not count towards the total page count.

3. Potential Project Impact & Value Proposition

Summarize the impact of the proposed project to the overall goals and objectives of NIIMBL and describe the overall value proposition. This should be from the perspective of NIIMBL, as well as the broader NIIMBL community and/or the United States biopharmaceutical manufacturing industry. Show how the project will advance the BRL of the technology by addressing the questionnaire for exit from the current BRL. Examples of impact include technical impact on productivity, quality, efficiency, energy usage, efficacy, potency, safety, and/or any other important factors identified in the key areas below (see Section 6). Economic impact in this sector might include factors such as scalability of technical 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.

4. Description of Team

Identify the Principal Investigator (PI) from the lead organization for the project proposal team, the co-PIs from partner organizations, and other senior/key personnel. In addition, each project team must identify a Project Manager to manage and oversee the project execution. The project manager should not be the PI for the project. 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.

NOTE: 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. Postdoctoral or graduate students or laboratory technicians should not be considered senior/key personnel. For all identified team members, include their responsibilities and roles in the project.

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 as prescribed in PAPPG 20-1: https://www.nsf.gov/bfa/dias/policy/nsfapprovedformats/biosketch.pdf

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 and must be submitted as a .ppt or .pptx file. The NIIMBL template is available at: http://www.niimbl.org/project-call-4-1.

Appendix C: **Project Plan - Work Breakdown Structure, Responsibilities Assignment Matrix, and Gantt Chart**

The 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. The Gantt chart will visually show how the work will be completed over time. One Project Plan is required for each project proposal team and must include all proposed work. The Project Plan must be submitted as a .doc or .docx file. A template is available for download at: http://www.niimbl.org/project-call-4-1

Appendix D: **Individual Organization Budget/Cost Justification**

Provide individual budget table (.xlsx) and cost justification (.docx) for the lead organization and each of the partner organizations requesting funding and/or committing cost share (including leveraged commitment) 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 forms. The budget template and separate cost justification template are available for download at: http://www.niimbl.org/project-call-4-1.

Project teams are encouraged to budget for travel to a kickoff meeting and to present at the NIIMBL National Meeting, which occurs in spring in Washington, D.C.

Appendix E: **BRL Questionnaire**

Answer each of the questions in the provided template regarding the NIIMBL Biomanufacturing Readiness Level(s) of the key aspects of the technology to be

demonstrated in the proposed work (instructions included with template). Supporting documentation, if needed, must be available upon request by NIIMBL. The BRL Questionnaire is available for download at: http://www.niimbl.org/project-call-4-1.

Additional Proposal Appendices

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: **Tier 3 industry member partner exemption request**

If a Tier 3 Industry Member is not a proposed project partner, then a required explanation must be submitted with the full proposal. The exemption request contains two components: 1. How do you know that there is no Tier 3 industry member available for this project? 2. The basis upon which it was determined to be fair and reasonable not to include a Tier 3 industry member. If a Tier 3 industry member is part of the project team, this appendix is N/A. A template is available for download at: http://www.niimbl.org/project-call-4-1

Appendix I: **Commitment Letters**

Include Letters of Commitment from (a) volunteer participating organizations essential to complete the project or from an end user of the developed technology; (b) large industry members who are only committing leveraged cost share; (c) state cost share commitments. If Commitment Letter(s) are not needed, this appendix is N/A.

4. Proposal Review and Evaluation

4.1 Stage 1: Concept Evaluation Criteria

NIIMBL Acceptance Criteria

Concept Papers and Concept Slide Decks must comply with requirements outlined in this RFP. Concepts will be non-compliant and not considered further if they include either a Concept Paper the exceeds the maximum 4 pages or a Concept Slide Deck that exceeds the maximum 5 slides. All administrative requirements, terms and conditions, and other appropriate disclosures will be assessed for completeness.

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

Concept Paper and Concept Slide Deck Review

NIIMBL will review submitted Concepts to ensure alignment with the NIIMBL mission (see Section 1 of this RFP), suitability of work within the BRL 4-7 space, and industry interest.

A panel of NIIMBL industry members and Federal stakeholders will be selected to review concepts and provide feedback to NIIMBL that will be used to prioritize a subset of Concepts for invitation to Full Proposals.

For technical projects, the Concept Phase evaluation criteria are:

1. The Concept's ability to address the topic's problem statement and a relevant industrial need.
2. The Concept's demonstration of awareness of existing solutions.
3. The Concept's ability to provide a clear value proposition for the project team, the broader NIIMBL community, and/or the biopharmaceutical manufacturing industry.
4. The BRL of the Concept falling within the NIIMBL mission space.

4.2 Stage 2: Full Proposal Evaluation Criteria

NIIMBL Acceptance Criteria

Full Proposals must comply with information requirements outlined in this RFP. 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 also reserves the right to request information regarding senior/key personnel's current and pending support after the submission of the full proposal. By requesting this information, NIIMBL will be able to better assess the capability of the senior/key personnel to conduct the proposed scope of work.

Automatic rejection will occur if (a) the submission is received after the published deadline; (b) the project team includes only a single member organization; (c) budget parameters are not met, such as the maximum project budget and minimum cost share ratio.

NIIMBL Subject Matter Expert Review Panel

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

Impact – 40%

- The proposal's ability to provide a solution to an industrial need.
- The proposed solution's difference than or complementarity to existing solutions or related initiatives.
- The speed with which the benefits of the project be realized.
- The proposal's ability to provide a clear value proposition for the project team, the broader NIIMBL community, and/or the biopharmaceutical manufacturing industry.

Technical Assessment – 60%

- The merit of the technical approach.
- Whether the project deliverables and timelines are realistic.
- The project's clarity of criteria for success.
- The team's inclusion of the needed technical expertise, including project management.

NIIMBL Technical Activities Committee

The NIIMBL Technical Activities Committee will perform an impact review using the following criteria:

- The proposal's ability to provide a solution to an industrial need.
- Whether the technical approach and project plan are likely to result in success.
- The proposal's ability to provide a benefit to NIIMBL members.
- Whether the project complements the existing NIIMBL technology portfolio.
- Whether the initial/final BRL falls within the NIIMBL mission space.

NIIMBL Governing Committee

The NIIMBL Governing Committee will take into account the total Project Call 4.1 funding that is available and perform a strategic review of the proposals. The GC will consider the following:

- Benefit to NIIMBL members
- NIIMBL sustainability
- Complementarity to existing NIIMBL project portfolio
- Cost and scope alignment with proposed benefits
- Cost share commitment
- Industry involvement

5. Reporting

Project reporting requirements will be outlined in the Project Award Agreement.

6. Project Call 4.1 Topics

Project Call 4.1 technical topic areas were informed by the results of feedback from subject matter experts amongst industry and academic members, and federal stakeholders. 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, the option to include individuals in these organizations should be considered. The narratives for each of the project topic areas below are not meant to be exhaustive. All approaches and concepts consistent with the overall goals described in the project topic areas will be considered.

1. Analytical technologies for vector manufacturing

Novel process analytical technologies (PAT) are needed to provide vector manufacturers with more timely measurement of process and product impurities, important process parameters and critical quality attributes. Proposals should consider how the sensor or analytical method information would be used as well as the timescales that would be required. This will allow us to focus on technologies that will have the most impact. Sensors or analytical methods that can be applied to allow better control of current processes and enable future intensified processes are of interest. Because of the increase in use of gamma-irradiated single use systems, compatible single-use, robust sensors for a wide range of process parameters that do not require calibration are needed.

2. Cell processing technologies and analytical technologies for live cell products (cell therapies)

Manufacturers are interested in the development of novel bioreactors as well as scale-down models for allogeneic operation. Rather than rely on cell culture platforms developed for protein and vaccine manufacture, 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.

Manufacturers are also interested in automated RNA and DNA extraction devices for online nucleic acid measurements of cultured cells in a bioreactor to monitor and control transfection. Custom bioreactors capable of culturing 5-50 x 10^6 cells/ml for T-cell manipulations (selection, activation, transduction) with low shear stress, high mass transfer capability, pH and O_2 control, closed loop control and integrated on-line, in-line sensors for measuring metabolites and for performing cell characterization are needed. Manufacturers have interest in self-contained analytical platforms that may include molecular methods such as qPCR, cell-based assays, mass spectrometry and flow cytometry or an adequate replacement. There is also a need for efficient gene transfection platforms that overcome the issue of diffusion and maintain high level of process control (e.g. gene copies /cell). Manufacturers are interested in cell washing/concentration technologies that enable > 3 logs removal of residuals, small volume holdup (0.25-10 ml) and that work at high cell densities (15-30x10^6 cells/ml). 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 also of interest to identify and chemically synthesize small, inexpensive molecules such as peptides that can bind to T cell receptors and replace expensive recombinant growth factors. 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.

Manufacturers have interest in novel analytical methods for understanding cell state composition, cell morphology and correlating phenotype with function. One of the most critical challenges for cell therapy manufacturers is identification and measurement of Critical Quality Attributes (CQAs). Analytical methods should ideally be non-invasive, label-free, involve small sample volumes, high-throughput and be sensitive enough to distinguish between a single cell and a population of cells. There is also a need for surrogate and appropriate reference materials.

3. Technologies for intensified processing of therapeutic proteins

Continuous processing can dramatically reduce the manufacturing footprint in a plant, increase productivity, and reduce the costs of energy and raw materials. This enables new facilities to be built with much lower capital costs or existing facilities to produce more and avoid having to build new facilities. Our measure for intensification for a unit operation is volumetric productivity, defined as the product throughput divided by the total volume of equipment (including tanks) required for the unit operation, measured in kg/yr/m^3. We are looking for technologies that allow significant (e.g. 50 to 100% or more) improvement in this measure over the state of the art.

Manufacturers have expressed interested in the following technologies in particular:

- Improved CHO cell lines that are engineered to perform in perfusion culture
- CHO cell lines engineered to grow to high density with higher productivity in simpler media
- Engineered "clean" CHO,; reduced or eliminated permissivity for MVM and other common adventitious agents that reduces downstream footprint.
- Improved understanding of CHO biology that enables media to be developed which increases volumetric productivity of cell culture.
- Process control innovations that deliver substantial improvement in volumetric productivity.
- Truly continuous downstream unit operations, including countercurrent and flowthrough methods, including precipitation.
- Improved “multimodal” downstream unit operations that reduce the total number of operations
- Downstream processes that can flow directly to the next unit operation without hold tanks, adjustment of pH, conductivity, buffer, etc.

7. List of Acronyms

1. BRL: NIIMBL Biomanufacturing Readiness Level
2. CHO: Chinese Hamster Ovary Cells
3. Co-PI: Co-Principal Investigator
4. CQA: Critical Quality Attribute
5. DNA: Deoxyribonucleic Acid
6. FDP: Federal Demonstration Partnership
7. FFRDC: Federally Funded Research and Development Centers
8. GC: Governing Committee
9. NIIMBL: National Institute for Innovation in Manufacturing Biopharmaceuticals
10. NSF: National Science Foundation
11. PAPPG: Proposal & Award Policies & Procedures Guide

12. PAT: Process Analytical Technologies
13. PC4.1T: Project Call 4.1 Technical
14. PC4.1W: Project Call 4.1 Workforce
15. PC4.1G: Project Call 4.1 Global Health Fund
16. PI: Principal Investigator
17. RFP: Request for Proposals
18. RNA: Ribonucleic Acid
19. WBS: Work Breakdown Structure