The National Institute for Innovation in Manufacturing Biopharmaceuticals

Project Call 1.0
Request for Proposals

Proposals due: January 26, 2017

V11222017

NIIMBL

Table of Contents

1. About NIIMBL and Project Call 1.0

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.

This document details the topic areas of interest, eligibility criteria, and guidelines for proposal preparation and submission process. **This Project Call requests proposals that address technology and/or workforce development issues in biomanufacturing, or projects that integrate both of these topics.**

Successful proposals are expected to:

1. Address a pre-competitive technical challenge and/or advance or create a resource for workforce training
2. Demonstrate a high likelihood of success in the proposed period of performance based on the nature of the project, and the expertise and resources available
3. Articulate clear goals and implementation strategies, including realistic and measurable deliverables and milestones
4. Demonstrate opportunity for a return on investment for NIIMBL members, particularly industry members, for greatest impact

As a member of the Manufacturing USA network, NIIMBL funds Technology Development Projects at manufacturing readiness levels (MRL) 4-7. Additional details on MRL levels are provided in Section 3.1 below.

NIIMBL's technical space includes existing biopharmaceutical products (e.g. proteins, antibodies, vaccines, blood products, bi-specifics) and emerging biopharmaceutical products (e.g. gene therapies, cell therapies). The NIIMBL technical space addresses needs for production of drug substance, drug product, and process and product control, for both existing and emerging classes of products (see Section 2).

2. Project Types

This project call solicits proposals for both Institute-Wide Projects as well as Partner-Specific Projects[1]. License rights to intellectual property developed in Institute-Wide Projects and

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

Partner-Specific Projects are treated differently, therefore project teams should carefully review Article IV of the NIIMBL Bylaws before categorizing their project as either Institute-Wide or Partner-Specific. Project teams must identify their project as either Institute-Wide or Partner-Specific on the Project Call Cover Sheet. Such a designation will be reviewed prior to project authorization to ensure it is appropriate for the type of project being proposed.

Project teams must also identify their project as either a Technology Development Project, a Workforce Development Project, or a combination thereof, on the Project Call Cover Sheet. Project teams must also identify their project as applying either to Existing products, Emerging products, or both, on the Project Call Cover Sheet, as defined in this Project Call.[2]

This project call solicits Small and Large Proposals. Small proposals can (i) request a maximum $200,000 per year ($300,000 for an eighteen-month project) of NIIMBL funding and are required to meet a minimum 1:1 (partners:NIIMBL) cost share requirement and (ii) are not required to include a small-to-medium enterprise (SME) as a partner (see Section 3.3), but to the extent that SME(s) are included as part of the project team and/or additional cost share is committed from partners, these proposals will receive additional points according to the rubric provided in Section 7.2 ("Small proposals"). Large proposals can (i) request more than $200,000 per year ($300,000 for an eighteen-month project) up to $1,000,000 per year ($1,500,000 for an eighteen-month project) of NIIMBL funding and are required to meet a minimum of 1.25:1 (partners:NIIMBL) cost share requirement and (ii) are required to include at least one SME as a Partner Organization (unless they meet one of the exemption criteria in section 3.3), but to the extent that additional SME(s) are included as part of the project team and/or additional cost share is committed from partners, these proposals will receive additional points according to the rubric provided for in Section 7.2 ("Large proposals"). Each proposal must be identified as Small or Large on the Project Call Cover Sheet.

This project call solicits proposals that fulfill the NIIMBL mission in critical areas of biopharmaceutical manufacturing through technology and/or workforce development projects. The technology development areas of interest were identified by compiling information from NIIMBL Tier 1 industry members, existing NIST Advanced Manufacturing Technology Consortia (AMTech) roadmaps,[3] and previous industry surveys conducted by NIIMBL. The workforce

---

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.

[2] "Emerging Products" are newly manufactured at clinical trial or commercial scale, and includes cell therapies and gene therapies, among others. "Existing Products" are commercially manufactured today and include therapeutic proteins, mAbs, vaccines, blood factors and components, and enzymes that are widely and commonly used to treat a variety of diseases.

[3] http://www.cellmanufacturingusa.org/national-cell-manufacturing-consortium

development areas of interest were identified through preliminary workforce surveys, presentations from NIIMBL industry members, and NIIMBL Teaming Meeting discussions.

Priority Funding Areas for this project call were identified and prioritized by the NIIMBL Technology Activities Committee and the Workforce Activities Committee, and are summarized in Section 9. The technology Priority Funding Areas, and the process by which they were prioritized, are described in Section 9.1. The workforce development Priority Topic Areas and the strategies of highest interest for addressing needs in these areas are described in Section 9.2.

Proposals submitted in response to this Project Call are not limited to the Priority Funding Areas outlined in Section 9; however, proposals that address a Priority Funding Area are likely to be ranked more favorably during review.

3. Eligibility Criteria

This section provides additional information on the criteria that will be used to determine whether project proposals comply with the requirements which determine eligibility for NIIMBL funding. The criteria which must be met address factors including MRLs, protection of human subjects, requirements on the composition of project teams, and cost share requirements.

3.1 Manufacturing Readiness Level[4]

NIIMBL seeks to accelerate the development of technologies that have promising applicability to key areas of need for the biopharmaceutical manufacturing community. NIIMBL-funded projects aim to advance technology in a measurable way; therefore, at the completion of a successful project, the final MRL will have advanced from the starting MRL. As a member of the Manufacturing USA Network, NIIMBL aims to fill the gap in manufacturing innovation between government and university research and the private sector, which occurs at MRLs 4-7, a space where technology is de-risked and studies are carried out to demonstrate the reliability and robustness of the technology in an industrially-relevant environment.

A technology falls within an MRL when it meets the requirements of that MRL. In the descriptions below, it is assumed that a given manufacturing technology comprises a *system* consisting of various *components*.

https://pharmahub.org/groups/lyo/lyohub_roadmapping

[4] "Manufacturing Readiness Level (MRL) Deskbook." Version 2.0 OSD Manufacturing Technology Program, May 2011. 2-2 –2-4 & Appendix A. *OSD Manufacturing Technology Program*. http://www.dodmrl.com/MRL_Deskbook_V2.pdf

MRL 1 & 2: Basic and applied research ideas with promise of specific solutions to address manufacturing challenges

MRL 3: Advanced development to establish proof-of-concept of these ideas in manufacturing

MRL 4: Capability to practice the technology in a laboratory environment (e.g. GLP) using industry relevant samples, standards and metrics

MRL 5: Capability of technology *components* to perform in a production-relevant environment (e.g. elements of GMP); Limit testing and performance characteristics determined

MRL 6: Capability to practice the technology *system* in a production-relevant environment; Performance is validated and confirmed

MRL 7: Capability to practice the technology in a production-representative environment (e.g. clinical batches, GMP) and pilot scale production demonstrated

MRL 8: Low rate production demonstrated; capability in place to begin full rate production

MRL 9 & 10: Capability full rate production; lean production practices in place

A **production-relevant** environment incorporates key elements of production realism, such as personnel, materials, equipment, processes, or work instructions, and may occur in a laboratory or model facility if key elements of production realism are added.

A **production-representative** environment is typically found on the manufacturing floor and contains most of the key elements of production realism, such as personnel, materials, equipment, processes, work instructions, cleanliness, etc.

A **pilot** environment is typically on the manufacturing floor and incorporates all key elements of production realism and is required to generate product that meets design requirements in low rate production.

Proposed projects should be focused on technology development in the MRL 4 -7 range. It is expected that *proof-of-concept studies (MRL 3) will have been completed* prior to the start of the project. At the completion of a successful project, it is expected that the final MRL will be higher than the starting MRL for the technology innovation. For additional guidance, please reference the NIIMBL Manufacturing Readiness Level Guidance Document http://www.niimbl.org/Downloads/MRLGuidance.pdf.

3.2 Human Subjects Activities

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. Federal regulations identify six categories of activity that are exempt from these requirements. NIIMBL Project Call 1.0 will accept proposals that include human subjects activities that is classified as exempt according to the regulations. Proposals for non-exempt human subjects activities will not be considered in Project Call 1.0. Additional guidance related to the six exemption categories is provided in the NIIMBL Human Subjects Activities Guidance Document http://www.niimbl.org/Downloads/ExemptHumanSubjectsActivitiesGuidance.pdf and at the HHS website. Please note that final revisions to the Common Rule were issued by the Department of Health and Human Services and are expected to go into effect on January 19, 2018. NIIMBL will issue amended guidance for Project Call 1.0 in the event that the revisions go into effect while this RFP is open.

All institutional certifications of the activity as an exempt activity will be required before a Project Award Agreement is issued, but such certifications are not required with the full proposal submission. To facilitate timely project award execution, it is recommended that the proposal lead be fully prepared to initiate the institutional certification process well in advance of project award notification.

3.3 Project Team Composition and Teaming Resources

To participate on a project team, an organization must have signed the NIIMBL Membership Agreement by 5:00pm EST on January 12, 2018. This means that the organization must have returned their Membership Agreement, signed by their authorized representative, to NIIMBL prior to that time. Information on how to join NIIMBL is available at www.niimbl.org.

Proposals have a requirement to include at least one small-to-medium enterprise (SME), who have joined NIIMBL as a Tier 3 Industry member, on their project team unless one of the allowable exemptions below applies. Proposals with additional SME participation will receive additional points according to the rubric provided for in Section 7.2. The following are allowable exemptions:

1. Proposals that are identified as a Small proposal on the Project Call Cover Sheet, and meet the requirements of a Small proposal (see Section 2).
2. Proposals that are identified solely as a Workforce Development project on the Project Call Cover Sheet.

Every project team must identify a Lead Organization to coordinate the proposal preparation efforts, and the Lead Organization must identify a Principal Investigator (PI) for the project from their organization. The Lead Organization will serve as the primary point of contact with NIIMBL

for all technical matters, and will provide leadership in the award negotiation phase, and in execution of the proposed project ("Lead Organization"). All other participating organizations will serve as Partner Organizations if they are providing expertise or resources in the execution of the projects ("Partner Organizations"). The Lead Organization and Partner Organizations are not limited to organizations who are requesting funding directly from NIIMBL or committing cost share. However, the Lead and Partner Organizations must be NIIMBL members. Proposal teams are required to involve a minimum of two NIIMBL members (a Lead Organization and at least one Partner Organization). Although there will be a Lead Organization, NIIMBL will directly issue subawards to all Partner Organizations on a project team, as appropriate and applicable. Thus, project teams will have to plan for careful coordination to ensure that project participants meet their technical project obligations and that non-performance, or unsatisfactory performance, is addressed. The Lead Organization PI will be responsible for technical reports.

In addition to identifying the PI, each team is required to identify a Project Manager who will track progress and communicate with their assigned NIIMBL Technical Director and Program Manager. The team can budget for the Project Manager either as a direct NIIMBL cost or as cost share from a Lead or Partner Organization. The Project Manager will be named as a key person if an award is made, and the proposal evaluation will include a review of the proposed Project Manager's project management skills and background, and the budget for the position. See also Section 6.3.3.6 of this Project Call.

To facilitate the formation of project teams, NIIMBL has established a Community Portal, an on-line resource to facilitate the identification of relevant expertise for partnering purposes. Moreover, NIIMBL encourages organizations to attend teaming workshops. NIIMBL facilitates coordination and marketing of these events. Refer to the 'Events' tab in the Community Portal for information about scheduled teaming workshops. Individuals at NIIMBL member organizations can use the Community Portal to post information about their expertise and interests. If you wish to add a profile to the Community Portal, please email help@niimbl.org.

NIIMBL will host a webinar on Tuesday, December 5, 2017 at 2:30pm EST to offer details and answer questions related to this project. An FAQ will be posted at the website. Registration information for this webinar will be sent out the week of November 27, 2017 to the NIIMBL member email list, posted at the Community Portal, and made available at the www.niimbl.org website.

3.4 Cost Share Requirements

Each project proposal must offer the required minimum cost share commitment. As described in Section 2, for Small proposals, the minimum requirement is 1:1. For Large proposals, the minimum requirement is 1.25:1. All cost share must come from non-federal sources. Proposals that include additional cost share will receive additional points in accordance with the rubric in Section 7.2.

Respondents 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 are encouraged to start the cost-share planning early. Teams requesting State cost share funding may require additional review and approval from those State organizations to secure their commitment for cost share funding. Proposal teams who secure state funding are encouraged to include confirmation of the support as an optional appendix (see Section 6.3.5.1). Project teams must contact the appropriate State organization for additional information:

Delaware: Contact Marta Rosario (martar@udel.edu) by December 22, 2017 to request possible state cost share. The request should include a 1 paragraph description of the project, partners, planned approximate budget, and justification.

Massachusetts: Massachusetts applicants should submit a draft application to NIIMBLMA@masslifesciences.com by January 15, 2018. Applicants may need to present their proposal in person on January 18th to the Massachusetts Life Science Center.

North Carolina: Contact John Horowitz (jmhorowi@ncsu.edu) at the NC State Office of Research, Innovation and Economic Development. Requests need to reach this office by 5pm on December 15, 2017.

4. Deadlines

January 12, 2018 – All members of a proposal project team must have signed the NIIMBL membership agreement by 5:00pm Eastern Standard Time (EST) to be eligible for project participation.

January 16, 2018 – Notice of Intent (NOI) to submit a proposal is due by 5:00pm EST from the Lead Organization from each project team. NOIs must be submitted to projectcalls@niimbl.org using the NOI template. Download the template from http://www.niimbl.org/Downloads/PC1NOItemplate.docx. NOIs are non-binding in that the project title, scope, and partners may be changed after submission; however, proposals from project teams that do not submit an NOI will not be considered.

January 26, 2018 – Proposals are due by 5:00pm EST. Proposals must be submitted by project teams via the Box.com folder assigned by NIIMBL upon NOI submission. Specific guidance and

submission instructions can be found in Section 6 and on the NIIMBL website at http://www.niimbl.org/Downloads/PC1ProposalSubmissionInstructions.pdf.

March 2018 –Lead and Partner Organizations will be notified of NIIMBL's intention to fund the project. Award negotiations with NIIMBL regarding tasks and budgets may be required. Teams have 30 business days to finalize award negotiations with NIIMBL including the Project Specific Intellectual Property (IP) Management Plan.

NOTE: If award negotiations with NIIMBL are not finalized within 30 business days of issuance of a Project Award Agreement, NIIMBL reserves the right to withdraw the intent to fund.

April 1, 2018 – Earliest possible start date for funded projects.

5. Award Information

NIIMBL anticipates providing $8,000,000 to fund Technology Development and Workforce Development proposals under this Project Call. Approximately $1,500,000 will be reserved for Small proposals, and the remaining $6,500,000 will be reserved for Large proposals. However, the final distribution of funding to Small and Large proposals will be at the discretion of the Governing Committee.

Small proposals can request a maximum $200,000 per year ($300,000 for an eighteen-month project) of NIIMBL funding and are required to meet a minimum 1:1 cost share requirement. Large proposals may request more than $200,000 per year ($300,000 for an eighteen-month project) up to $1,000,000 per year ($1,500,000 for an eighteen-month project) of NIIMBL funding and are required to meet a minimum of 1.25:1 cost share requirement. Each proposal must be identified as Small or Large on the Project Call Cover Sheet. NIIMBL aims to fund a portfolio of impactful projects of various sizes, so project teams are encouraged to submit proposals with funding requests of any size, up to the maximum amount based on their proposal type. Proposals will be reviewed carefully for the project team's ability to carry out the scope of work within the performance period, may be asked to reduce or modify their scope of work after review, and will be required to support a Project Manager for the team. Projects are limited to no more than 18 months in duration.

All proposed costs, both in the requested budget and in the proposed cost share budget, must be deemed allowable in accordance with the Department of Commerce Standard Terms and

Conditions (March 2017)[5] and the Federal cost principles set forth in 2 CFR 200, Subpart E.[6] Examples of allowable costs include salaries and associated fringe benefits for personnel and students participating on the project, equipment, supplies, services, and travel in support of the project. In addition, federally negotiated indirect costs will be reimbursed in accordance with 2 CFR 200.414. Costs to support construction are not allowable. Costs to support renovations require prior approval. Project work should take place within the United States, and prior approval must be obtained for any activities taking place outside of the United States, including foreign travel. For inquiries related to cost share allowability, contact your organization's NIIMBL Program Manager (PM). You can find your PM in the NIIMBL Community Portal at niimbl.force.com.

Funding from NIIMBL will only be available to organizations and institutions that are Tier 1, 2, 3 and Affiliate Members, and have agreed to comply with all aspects of confidentiality and intellectual property considerations described in the NIIMBL Membership Agreement and Bylaws.

Overall project cost share is subject to the minimums described above (1:1 for Small proposals and 1.25:1 for Large proposals). Budgets are required to be proposed by Deliverable. While it is not *required* to meet the cost share minimums by deliverable, it is *recommended* that the budget meet such cost share minimums by deliverable. Proposals with budgets that do not meet the cost share minimums per deliverable will be accepted and reviewed; however, if selected for funding by the Governing Committee, NIIMBL reserves the right to negotiate the proposal budget in an effort to approach the minimum required cost share by deliverable.

Project Award Agreements will be issued in accordance with the NIIMBL Bylaws. NIIMBL will enter into a Project Award Agreement with all project team members, both funded and non-funded, in support of their efforts on the project. Adjustments to the proposed budget and tasks may be required, depending on guidance provided by the reviewers and the Governing Committee.

---

[5] http://www.osec.doc.gov/oam/grants_management/policy/documents/Department%20of%20Commerce%20Standard%20Terms%20&%20Conditions%2031%20March%202017.pdf

[6] http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title02/2cfr200_main_02.tpl

6. Proposal Preparation and Submission Process

6.1 Notice of Intent

The Lead Organization of each project team is required to send a NOI to submit a project proposal. The notice must be submitted via email to projectcalls@niimbl.org by 5:00pm EST on January 16, 2018. The notice must include the following: the names of expected Lead and Partner Organizations, a draft proposal title, the names and contact information for all individuals requiring access to the project team's Box submission folder, and a 200-word summary of the proposed work. While the NOI is required, the information it contains about partners, the title, and the ultimate submission of a project proposal is non-binding. Changes can be made to the list of Partner Organizations; however, NIIMBL must be notified if the Lead and/or Partner Organizations change and/or if changes in access to the project team's Box.com folder are required. The Lead Organization must communicate changes to the NOI via email to projectcalls@niimbl.org before Wednesday January 24, 2018 at 5:00 pm EST.

Upon submission of the NOI, NIIMBL will create a private, secure folder on Box.com that is accessible only to team personnel from organizations named in the NOI and NIIMBL personnel. All users will have full read/write access to the folder to permit for document upload, download, and deletion.

6.2 Proposal Submission

The full proposal must be uploaded to the project team's Box folder by 5:00pm EST, January 26, 2018. The full proposal must be in the form of **a single pdf file** and must consist of the combined elements 1-5 outlined below, with the exception of the Individual Organization Budget workbooks, which must be uploaded separately as an .xls or .xlsx file. Specific guidance and instructions for completion of these elements are provided on the NIIMBL website at http://www.niimbl.org/Downloads/PC1ProposalSubmissionInstructions.pdf.

No changes or edits may be made to any submitted proposal documents after the deadline (5:00pm EST, January 26, 2018) unless they are expressly requested and authorized as part of the compliance review (see Section 7.1). At the submission deadline, NIIMBL will convert user access to the folder to View Only. Any changes to the documents occurring after 5:00pm EST on January 26, 2018 will not be accepted.

6.3 Proposal Elements

Each submission includes 4 required proposal elements, listed below as items 1-4. Submissions may elect to submit optional proposal appendices, listed below as item 5. No additional information will be permitted. Proposals which fail to comply with all required proposal elements will be excluded from consideration for award and will not be reviewed. To assist in

the proposal preparation, a compliance check sheet can be found at http://www.niimbl.org/Downloads/PC1ComplianceCheckSheet.pdf.

1. Project Call Cover sheet(s)
2. Abstract
3. Proposal Narrative
    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
    1. References
    2. List of Acronyms
    3. Biosketches
    4. Quad Chart
    5. Work Breakdown Structure
    6. Individual Organization Budgets
    7. Consolidated Budget
5. Optional Proposal Appendices
    Letters of commitment

6.3.1 Project Call Cover Sheet

The Lead Organization and each Partner Organization, including organizations that are not requesting funding, must complete their own Project Call Cover Sheet. The Lead Organization and each Partner Organization must be NIIMBL members, and are identified as organizations providing expertise or resources in the execution of the project. The Lead Organization and Partner Organizations are not limited to organizations who are requesting funding directly from NIIMBL or committing cost share. Download the template from http://www.niimbl.org/Downloads/PC1ProposalCoverSheet.pdf and complete all required fields.

6.3.2 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 and may be shared publically by NIIMBL; therefore, please ensure that the brief description does not contain any confidential or proprietary information. Download the template from http://www.niimbl.org/Downloads/PC1AbstractTemplate.docx and complete all required fields.

6.3.3 Proposal Narrative

The proposal narrative must be single-spaced, 11 point *Arial* font (or larger equivalent font) with 1" margins and numbered pages. The font limitations do not apply to figures or tables. The proposal narrative must include all the sections described below and must not exceed 15 pages (including the Executive Summary).

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

   Summarize the proposed work, the technology or workforce development objectives and how they are consistent with NIIMBL goals, MRLs, and the projected impact of the project. The Executive Summary is confidential and is limited to one page.

2. *Background and Significance*

   Describe the problem being addressed. Summarize prior work done in the area, preliminary results, and the starting/ending MRLs of the work being proposed. The Background and Significance section should also summarize the overall objectives of the project, regulatory considerations, and significance of this project for the industry.

3. *Project Description*

   Describe the activities or workforce development methodologies and approaches to be used. The Project Description must align with the Work Breakdown Structure, which is a required appendix (see section 6.3.4.5). The Project Description provides additional details related to the tasks to be completed by the Lead Organization and each Partner Organization, milestones, deliverables, go/no-go decision points, and timelines. The Project Description must clearly delineate metrics for success.

4. *Potential Project Impact*

   Summarize the impact of the proposed project to the overall goals and objectives of NIIMBL. For example, describe any potential improvements in productivity, quality, efficiency, energy usage, efficacy, potency, safety, and/or any other important factors related to the production of biopharmaceuticals that may be derived from the project, as well as any impact on domestic competitiveness in this sector such as the development of a highly trained workforce, the future of domestic 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 team, the Co-PIs from Partner Organizations, other senior/key personnel, and the project 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 approaches to be taken to ensure that the work of the project team members will be synergistic and how information among the various team members will be shared. Describe how issues of material and technology transfer will be addressed and how progress on the project will be tracked. Note that while each project will be assigned a NIIMBL Technical Director to help facilitate and monitor project progress, project teams must also identify a Project Manager for their team. This section should include the name of the identified Project Manager and a description of their project management experience (including whether they are Project Management Institute-certified or working towards their certification). Note that the Project Manager does not have to be from the Lead organization and may be from one of the Partner organizations.

6.3.4 Required Proposal Appendices

1. *References*

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

2. *List of Acronyms*

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

3. *Biosketches*

Provide biosketches for the Lead Organization's PI and all Partner Organizations' co-PIs. 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].

4. *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 http://www.niimbl.org/Downloads/PC1QuadChartTemplate.pptx.

5. *Work Breakdown Structure*

Complete a work breakdown structure (WBS) for the proposed project. This document forms the foundation of the proposed project plan. The project must be broken down by deliverable which must be further broken down into tasks and subtasks. Each task must include milestones, and the WBS must also include go/no-go decision points and a timeline. A Gantt chart must be included as part of the WBS and must include all elements of the WBS. One WBS is required for each project team and must include all proposed work. The WBS will be used to evaluate the scope of the proposed work and to measure progress of projects selected for funding. The WBS template is available for download at http://www.niimbl.org/Downloads/PC1WBSTemplate.docx.

6. *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 Deliverable as represented in the WBS. The budget template is available for download at http://www.niimbl.org/Downloads/PC1BudgetTemplate.xlsx. The budget template allows for 5 deliverables. Any project team with more than 5 deliverables is asked to email projectcalls@niimbl.org for further direction on how to complete the budget workbook.

7. *Consolidated Budget*

Compile all budgets from the Lead and Partner Organizations into a consolidated budget, using the NIIMBL Consolidated Budget template. The consolidated budget must be prepared by the Lead Organization, and should be organized by partner summarizing NIIMBL request, State cost share (if applicable), Partner Organization cost share, and total overall project budget. The consolidated budget template is available at http://www.niimbl.org/Downloads/PC1ConsolidatedBudgetSummary.xlsx. The consolidated budget must be included in the single PDF submission.

6.3.5 Optional Proposal Appendices

1. *Letters of Commitment*

Include any letters of commitment that the teams choose to include, if available and if applicable. It is expected that all commitments of support and/or resources are being made by NIIMBL member organizations; therefore, letters of commitment should only be submitted from these organizations.

7. Proposal Review and Evaluation

7.1 Compliance Review

To ensure complete, compliant proposals are forwarded for review and evaluation, an administrative review will be conducted on all full proposals to verify compliance with the requirements put forth in this RFP. Proposals that are found to be noncompliant may not be reviewed and considered for funding.

If instances of noncompliance are identified during the administrative review, project teams will be given the opportunity to correct administrative noncompliance, but only upon notification by NIIMBL. Under no circumstances will project teams have an opportunity to make any changes or corrections to the Project Narrative or the Work Breakdown Structure. No changes or alterations will be allowed to a submitted proposal after the deadline beyond those instances of noncompliance specifically identified by NIIMBL. If any otherwise complete proposal has extraneous information (extra pages or unallowed supplemental documents), that extraneous information will be redacted by NIIMBL to bring the proposal into compliance.

7.2 Proposal Scoring Criteria

Proposals will undergo a merit review, and will be scored using the following rubric:

1. *Project Significance: 25 points maximum*

   The extent to which the project addresses the NIIMBL mission. Also, the degree to which the project aligns with the characteristics of a successful Project as described in Section 1 of this RFP.

2. *Merit: 25 points maximum*

   Technical projects are based on sound scientific principles, fall within MRL 4-7 range, and provide clear and achievable milestones or deliverables. Workforce development projects are based on state-of-the-art approaches to training, have regional or national impact, and well-defined metrics for success.

3. *Project Potential for Impact on Industry: 30 points maximum*

   The likelihood for the project to realize significant and expeditious returns for the industry in productivity, quality, efficiency, energy savings, efficacy, potency, safety, economic impact and/or any other important factor related to the production of biopharmaceuticals. Workforce development projects should accelerate the training of a globally competitive biomanufacturing workforce.

4. Team Expertise: 20 points maximum

The degree to which the Lead Organization and all Partner Organizations, including the named individuals from those organizations, can provide the right environment, infrastructure, experience and expertise to successfully complete the project.

Following the merit review, additional points will be awarded if some/all of the following criteria apply and will be factored into the decision making by the Governing Committee:

1. The total amount of cost share in excess of the minimum

The minimum cost share requirement for Small proposals is 1:1, and the minimum cost share requirement for Large proposals is 1.25:1. However, if project teams commit greater than the minimum for their proposal type, they will be issued up to an additional 15 points maximum, for up to 2:1 cost share.

2. The degree of Tier 3 Industry member (SME) participation

Small proposals are not required to include SMEs on their project teams, and Large proposals are required to have a minimum of 1 SME on their project teams (unless they meet one of the exemption criteria in Section 3.3). However, if project teams include more than the minimum number of SMEs on their projects teams, they will be issued up to an additional 10 points: 5 points for one additional SME and 10 points for two or more additional SMEs. That is, a Small proposal with one SME will receive 5 points and a Small proposal with two SMEs will receive 10 points; a Large proposal with two SMEs will receive 5 points and one with three or more SMEs will receive 10 points.

8. Reporting

Reporting requirements will be outlined in the Project Award Agreement, but will involve both technical and financial reporting. Individuals and organizations on funded projects will be required to comply with the outlined reporting requests found in the Project Award Agreement.

9. Priority Funding Areas

Priority Funding Areas were identified and prioritized by the Technology Activities Committee and the Workforce Activities Committee as described below. The Priority Funding Areas consist of specific Technology Topics or Workforce Development Topics/Strategies of Interest. While proposals for this project call are not limited to the Priority Funding Areas described below, proposals that address a Priority Funding Area are likely to be ranked more favorably during proposal review.

9.1 Technology Priority Funding Areas

The NIIMBL Technical Activities Committee (TAC) was presented with a list of 30 technology topics which were grouped into eight General Topic Areas. TAC members prioritized the individual technology topics by providing a score for each technology topic of between 1 and 5 (where 1 indicated Low priority and 5 indicated High priority). In accordance with the TAC Charter, the votes of Industry Members were weighted to represent two-thirds (2/3) of the final (aggregate) score, and the votes of all other Members were weighted to represent the remaining one-third (1/3) of the final (aggregate) score. The final (aggregate) score for each technology topic is considered the Priority score. The highest Priority score across all the topics was 4.1 and lowest score was 2.5. The Technology topics under each General Topic Area have been ranked based on the Priority scores.

9.1.1 Improved Analytical Technologies

1. *PAT for Real-time Drug Substance and Drug Product Release (Priority score - 4.1)*

   Develop novel process analytical technologies (PAT) that provide manufacturers with in-line, on-line, or at-line measurements of critical process parameters or critical product quality attributes that enable real-time process control or real-time product release. Analytical testing currently causes significant delays in release of drug substance and drug product release due to the time it takes to complete often the complex and comprehensive characterization testing needed to ensure product identity, purity, and potency. The ideal state for manufacturers would be real-time measurement of critical process parameters or critical product quality attributes to enable release of drug product or drug substance in dramatically reduced time frames.

2. *Rapid Adventitious Agent Testing (Priority score – 3.7)*

   Develop rapid analytical methods for faster detection of microbial, mycoplasma, and/or viral contaminants for raw materials, for final product testing or testing in process, with results available within 24-48 hours. Current compendial methods used for adventitious agent testing are time-consuming, with culture-based testing taking up to 28 days. More rapid analytical methods would benefit manufacturers of emerging products like cell and gene-modified cell therapies, which may have short shelf-lives that preclude obtaining results of sterility testing prior to administration. Manufacturers of established biotherapeutics would benefit from rapid adventitious agent detection that could be used to enable real-time release and/or improve process trouble-shooting. Projects focused on this topic should include demonstration that the newly developed technology is equivalent to compendial methods.

3. *Improved Host Cell Protein Detection/Analysis (Priority score – 3.6)*

   Develop novel analytical methods for in-line or at-line measurement and identification of host cell protein in protein and mAb manufacturing. Residual HCP is an important

product quality attribute because of the potential to cause immunological reaction in the patient. Current HCP analytical methods can be complex, time-consuming, and off-line. New analytics for HCP analysis will be in-line or at-line tools that provide quantitation and identification of HCP species. The industry would also benefit from standardization of HCP methods and reporting across the industry.

4. *Novel Methods for Characterization of Live Cell Products (Priority score – 3.1)*

   Develop novel analytical methods for "meaningful-omics" analysis of live cells for cell therapy products. One of the most critical challenges for cell therapy manufacturers is characterization of highly complex products and the need for a 'heat map' approach to characterize live cells that can be correlated directly to the observed effects on the patient. The 'heat map' might include any number of measurements of cell characteristics which taken together, and weighted in novel ways, will relate to patient outcomes.

5. *Novel Methods for Detection/Quantification of Product Sequence Variants (Priority score – 3.0)*

   Develop real-time analytical methods for monitoring sequence variants for protein and monoclonal antibody products. Biopharmaceutical manufacturers are currently pursuing development of highly intensified modes of bioreactor operations with increased specific productivity. Unfortunately, as protein expression levels are increased, fidelity of protein synthesis tends to decrease, leading to increased product heterogeneity. Manufacturers would benefit from development of real-time (at-line or in-line) analytical technologies for rapid measurement of sequence variants in the bioreactor, which will be present at a low level compared to the desired product. Real-time measurements of sequence variants could be integrated with additional measurements of process parameters, as well as -omics data, to allow for adaptive process control of product sequence variants and increased product quality.

6. *Technology for Demasking Low Endotoxin Recovery (Priority score – 2.5)*

   Develop a general over-arching solution to the problem of LER which has wide applicability to a broad range of biologic products, including proteins, monoclonal antibodies, vaccines, and cell and gene therapy products. The phenomenon of low endotoxin recovery (LER) has been observed in spiking studies of undiluted protein and monoclonal antibody drugs carried out to validate the bacterial endotoxin test, and is thought to be related to the drug excipient composition. The result is a "masking effect" that keeps endotoxin in the sample from reacting with Factor C in the Limulus Amebocyte Lysate (LAL) test. Because resolution of this phenomenon is typically product-specific, finding the solution can be resource intensive and the solution may not translate to other products, with different drug and excipient properties. An over-arching solution to this problem would be of great interest.

9.1.2 Drug Substance Manufacturing – Upstream

1. *Cell Line Development and Engineering (Priority score – 3.6)*

Develop novel cell lines that have increased productivity 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. CHO specific productivity has increased over 1000-fold since the first product manufactured in CHO was approved in 1987. Use of CHO imposes limitations, however, due to the slow growth rate and shear sensitivity. New cell lines, either CHO or other, will 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 approach is to consider the development of novel host cells that are smaller and allow for increasing cell density in the bioreactor, can perform post-translational modifications, and have a sufficiently high specific production rate that will yield to significant increases in productivity (increased titers). Other potential side benefits might include a reduction in HCP, ease of downstream operation, and a reduction of virus-like particles.

2. *Cell Banking Technology Development (Priority score – 3.1)*

Develop improved technologies for automated filling and sealing of sterile glass ampoules. The most critical operation in cell banking is the rapid filling, sealing, and freezing of cell suspension aliquots after cryoprotectant is added to the harvested cell suspension. Master and working cell banks are often stored directly in liquid nitrogen (LN_2) to avoid temperature fluctuations which can occur in vapor-phase LN_2 storage. Glass ampoules are preferred for storage directly in LN_2 as the seal precludes entry of LN_2 and the subsequent explosive expansion of trapped gas upon thaw. Glass ampoules, however, have been less amenable to automated filling and sealing operations than plastic cryovials. A rapid, robust, easy way to validate platform for automated filling and sealing of glass ampoules is of great interest to industry.

9.1.3 Drug Substance Manufacturing – Downstream

1. *Technology Development for High Density CHO Harvest (Priority score – 4.1)*

Develop novel disposable harvest unit operations for efficient and robust harvest of high-density CHO cultures, ideally using disposable materials. The traditional harvest methods for CHO culture such as centrifugation, tangential-flow filtration (TFF) or depth filtration are very difficult to apply to the high-density CHO cultures being reached in perfusion or continuous cultures. Alternative methods of solid-liquid separation are needed. In addition, manufacturers would like to ensure that these new operations can

be carried out using disposable technologies, such as are increasingly being used for upstream and downstream operations, to facilitate process continuity and connectivity.

2. *Bulk Drug Substance Storage and Freezing Technology Development (Priority score – 3.8)*

   Develop single-use systems and novel bulk storage methods for storage of large volumes of bulk drug substance or bioreactor harvest. Manufacturers often store large volumes of bioprocess liquids in a frozen state. Often this can be drug substance, or a process intermediate, which can be stored for extended periods of time prior to subsequent purification or drug product formulation. Increasingly, this can be reactor harvest volumes, as continuous and perfusion modes of upstream operation become more common. Uniform freezing and thawing of large volumes of liquids containing biological products is quite challenging, because non-uniformity in temperature and concentration gradients can negatively impact product quality, especially for highly concentrated or less stable products. Manufacturers would like to extend the use of disposable systems from upstream and downstream processing into their bulk liquid storage operations. Potential approaches might include novel technologies based on lyophilization, spray drying, precipitation and crystallization.

3. *Drug Substance Manufacturing - Chromatography Technology Development (Priority score – 3.2)*

   Develop technologies for downstream recovery of protein biotherapeutic products that are low cost, can handle very high titers, and are amenable to integration into continuous manufacturing operations and single-use disposable operations. The major costs of downstream protein and mAb manufacturing operations are the affinity chromatography resins used to separate the desired product from the cell culture broth. There are several options for decreasing these costs, ranging from development of improved resins to replacement of the chromatography steps with novel unit operations which achieve the desired product separation. The goal of this topic is to reduce the cost-of-goods for downstream recovery and purification of protein biotherapeutics. Examples of the kinds of projects include optimized resins that would be less expensive, reduce residence times, and thus increase throughput. Modified chromatographic approaches that focus on negative or flow-through chromatography to reduce bind and elute steps can also result in significant savings, as high-throughput, high-capacity membranes that can operate at very short residence times because of low diffusional limitations.

4. *Viral Clearance Technology Development (Priority score – 2.7)*

   Develop novel 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. Additionally, these unit

operations are generally not applicable to manufacturing of emerging therapeutics such as cell therapy products and gene therapy vectors. Continuous approaches to viral clearance may also lead to novel approaches for the production of viral vectors for gene therapy and virus-free cell therapy products.

9.1.4 Drug Substance Manufacturing – Integrated Process/Platform Development

1. *Continuous Processing Technology Development – Biologics (Priority score – 4.1)*

Develop novel manufacturing platforms for continuous unit operations as well as for integration of continuous upstream and downstream operations. High volume biopharmaceuticals made in very large batches to handle the needs for large dosages and/or increased patient populations are potential candidates for conversion from single-batch processes to continuous or hybrid processes where the upstream and downstream steps are connected and product can be collected in an essentially continuous process. This process concept can take on various manifestations from integrating or connecting upstream and downstream steps, or two downstream steps to act continuously, or developing total new technologies that enable continuous manufacturing of even a section of the process. Continuous processes will require novel in-line or on-line sensors or detectors for process measurements and product quality as well as feedback control mechanisms and approaches that can help ensure batch quality and facilitate validation of product created over a long period of time with potential time-to-time variations within proper operating windows during processing.

2. *Scale-down Models for Improved Manufacturing Process Development (Priority score – 3.9)*

Develop scale-down models of continuous manufacturing processes and cell therapy manufacturing processes to enable more rapid and cost-effective process development activities. Biopharmaceutical manufacturers rely on scale-down models of the manufacturing process to determine the impact of operating variables on process performance and product quality. While acceptable scale-down models are available for traditional batch bioreactors, there are not optimized scale-down models which can accurately recapitulate intensified and/or continuous bioreactor operations used in perfusion or continuous operating modes. In long-term bioreactor operations, the volume of media consumed even at small scale operations can be a barrier to performing sufficient number of experiments. In other cases, such as the cell and gene therapies, fit-for-purpose bioreactors may have configurations which are not reproduced in current scale-down models and therefore, novel scale-down configurations are needed to enable process development activities for these products.

3. *Manufacturing Platforms for Cell Therapy Products (Priority score – 3.5)*

   Develop novel bioreactors for cell therapy manufacturing applications. Cell therapy manufacturing has often repurposed off-the-shelf equipment rather than developing optimized bioreactors for their operations. Manufacturers are interested in developing 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.

4. *Cost-Effective Gene Vector Production (Priority score – 3.2)*

   Develop a cost-effective procedure for gene vector production. The production of gene therapy vectors is often one of the costliest parts of manufacturing for clinical trials and commercial-grade gene 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 which would enable them increased flexibility in the site of vector production.

9.1.5 Drug Product Formulation Technologies

1. *Improved Lyophilization Technologies (Priority score – 3.5)*

   Develop novel, scalable lyophilization processes that are amenable to higher throughput applications. Lyophilization technology has been commonly used for freeze-drying final drug product, most often in glass vials with rubber stoppers. The lyophilization process depends upon uniformity and tight control of the process temperature and pressure. Manufacturers are interested in scaling up lyophilization operation to large lot sizes and also to applications where drug product throughput is increased, such as in continuous operations. Improvements in sensor technology as well as development of novel unit operations are of interest.

2. *Particulate Detection and Resolution Technology Development (Priority score – 3.4)*

   Develop in-line, on-line, or at-line tools for measurement of visible and sub-visible particulates in biotherapeutic products, and global particle standards for these new methods. The presence of particulates in biotherapeutic drugs poses risks to the patient, whether the particulates are protein aggregates which can cause an immunological response, or inorganic matter derived from disposable, single-use materials that was not intended for human administration. Accurate detection and identification of particulate levels allows appropriate disposition of the finished drug

product, as well as an opportunity to affect process changes to control particulates at an acceptable level. These tools should be able to detect particulates in the sub micron range, and to completely distinguish particulates from intact cells. Development of appropriate global standard materials to enable validation of these novel particulate detection methods is also of interest.

3. *Development of Drug-Stability Models (Priority score – 3.1)*

   Development of improved predictive models for demonstration of drug product stability under stressed conditions. Drug product stability protocols typically require some forced degradation (stress) testing; however, the regulatory guidance around how to carry out this testing is sometimes considered to be relatively vague. These tests can be very helpful in determining the degradation pathways, degradation products, and consequently, what stability-indicating test methods will be required. This information can also be useful for formulation development. Manufacturers would like to develop improved models for heat and chemical stress as well as potential resistance to proteases and high concentrations.

4. *Improved Cryopreservation or Cell Preservation Technologies (Priority score – 3.1)*

   Develop alternatives to dimethylsulfoxide (DMSO) for cell therapy products. DMSO is frequently used to cryopreserve cell therapy products; however, DMSO is cytotoxic, posing severe limitations on the time allowed for cell harvesting and cryopreservation operations, as well as requiring strict freezing protocols, and also has compatibility issues with some container types. Manufacturers would like to see development of alternative cryoprotectants. More dramatic changes to cell preservation technology, such as room temperature storage or cell product spray drying or lyophilization would also be of interest.

5. *Improved Platforms for Streamlining Operations for High Dose/High Volume Products Delivered in IV Bags (Priority score – 2.8)*

   Develop novel platforms for manufacturing operations involving handling drug product delivered in IV bags in the final configuration. Many of the newer biologic products are packaged into a final product configuration utilizing IV bags prior to administration to the patient. Often these products have a very high drug concentration, with resulting high viscosity which imposes handling restriction. Manufacturers are interested in developing manufacturing operations which will enable more streamlined handling of these IV based system.

9.1.6 Novel Materials for Manufacturing

1. *Disposable Technology Development for Drug Product and Drug Substance (Priority score – 3.3)*

   Develop (1) improved materials for single-use biomanufacturing that have acceptable levels of leachables, extractables and particulates for a range of single use applications, and (2) improved methods for integrity testing of disposable bags and tubing. Single-use technologies are widely used for biomanufacturing applications. Use of these materials has required development of suitable materials as well as test methods to demonstrate that they are acceptable for use in manufacturing. The materials used to manufacture the disposables must demostrate acceptable levels of leachables under the conditions that they are used in the manufacturing process. Improved materials with lower leachables, especially at extreme storage conditions, such as long-term elevated-temperature culture and frozen storage, are of interest to manufacturers. The structural integrity of these disposable materials must be verified prior to initiation of manufacturing operations, because small leaks can potentially result in the loss of an entire manufacturing run. Integrity is typically demonstrated by inflating the assembly with sterile gas and monitoring the pressure decay. Manufacturers would like an alternative integrity test which is rapid, robust, and potentially more sensitive than the pressure-decay methods.

2. *Silicone-free Syringes Compatible With Protein Solutions (Priority score – 2.9)*

   Develop a silicone-free syringe that is compatible with protein biologics and demonstrate that the device does not negatively impact drug product critical quality attributes and stability. Prefilled syringes are an increasingly important dosage form for biologic medicines because they can potentially reduce medication errors, eliminate potential contamination during syringe loading, and facilitate at-home administration. Silicone oil is typically used as a syringe lubricant; however, the silicone oil may migrate into the drug product. For protein biologics, this can cause conformational changes and aggregation, and may also impact drug product stability. Syringe materials that can overcome these challenges would be a welcome addition to the product.

9.1.7 Process Modeling, Control & Automation

1. *Adaptive Process Control Development (Priority score – 4.1)*

   Develop adaptive process control algorithms based on *in situ* metabolite, product attribute or product quality measurements. Manufacturers would like to enable closed-loop, adaptive process control (APC) for biomanufacturing processes. This goal is enabled by advances in Process Analytical Technologies (PAT) that provide real-time measurement of critical process parameters and product quality attributes and predictive mechanistic models which can be used to develop control algorithms based

on these measurements. Advanced PAT and APC will enable better definition of the design spaces for Quality by Design (QbD) applications and provide increase security to the biotherapeutic supply chain by providing earlier identification and correction of process deviations. This topic is closely related to **Topic 9.1.1.1** above.

2. *Unit Operation Mechanistic Model Development (Priority score – 3.9)*

   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 the practice of factorial design models. One example would be models of mixed-mode chromatography and overload / elution chromatography that can be used for future feedback control of manufacturing operations. Another example 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.

3. *Multivariate Analysis for Process Modeling and Control (Priority score – 3.8)*

   Develop platforms to allow multivariate analysis (MVA) of process and product data 24/7 at world-wide manufacturing sites for increased process control and improved process model generation. Many biomanufacturers have on-going efforts in multivariate analysis to increase process understanding and control. There are also significant other benefits to data-intensive MVA efforts, such as the generation of better process models. Manufacturing data is often generated 24/7 through world-wide operations, and would ideally be analyzed in real-time to facilitate process control. MVA is often a significant effort in terms of time and resources, with the value added often not being apparent in the short term. Improved tools for MVA, as well as potentially collaborative industry-wide efforts at defining a standard MVA approach would add value to manufacturing operations.

4. *Standardized Data Structure (Priority score – 3.6)*

   Develop a standardized data structure to enable communications between manufacturers, CDMOs, and regulators to facilitate data sharing and filing of license applications. The biopharmaceutical manufacturing process generates a very large amount of data from both in-house operations and off-site collaborators. The types of data being collected includes real-time measurements of process parameters, the output of instruments used in off-line analytical testing from both in-house and off-site laboratories, measurements related to facility and environmental operations, and electronic documents such as batch records used to record operational information. This data can also be generated at multiple geographic sites. Standardization of the data structure used to generate and store manufacturing-related data would facilitate interactions between all of the entities involved in these operations, as well as

potentially facilitate easier filing and review of license applications which contain data from multiple sources. It could also facilitate process and product understanding and potentially improve process control and product quality. This topic is closely related to **Topic 9.1.7.3**.

9.1.8 Regulatory Science & Standards

1. *Connection of Manufacturing Data with Clinical Performance (Priority score – 3.2)*

   Develop methods for connecting manufacturing process data or product quality attributes to clinical performance of cell therapy drugs. One of the most challenging aspects of manufacturing cell therapy products is determining which process parameters and product quality attributes are connected to clinical performance of the drug. Manufacturers would be interested in developing data analytics or tracking procedures that would enable them to mine available data and determine whether any conclusions can be drawn about regarding critical parameters. This project is related to **Topic 9.1.1.4** above.

2. *Regulatory Harmonization of Quality by Design Approach (Priority score – 3.1)*

   Develop a harmonized framework for QbD that is acceptable to worldwide regulatory agencies. Manufacturers are being encouraged by regulatory authorities to use Quality by Design (QbD) procedures to ensure manufacturing robustness and product quality. The US FDA approach to QbD differs in some respects from that of the EMA and other extra-US agencies. As biopharmaceutical manufacturers are multi-national organizations, harmonization of these approaches would be beneficial. Manufacturers are also interested in application of QbD approaches to cell and gene therapy manufacturing operations. As one example, **Topic 9.1.1.3** addresses the need for standardization of HCP characterization technologies and this could be a suitable topic for global harmonization discussions.

3. *Process Validation for Autologous Products (Priority score – 2.9)*

   Develop universal validation protocol for autologous cell therapy products. Autologous cell therapy manufacturing operations are characterized by high degrees of variability due to patient-related diversity. This can cause significant challenges in validation of the therapeutic product. Novel mechanistic or statistical approaches that can help streamline the validation process by properly accounting for these deviations in the process space would be welcome.

9.2 Workforce Development Priority Funding Areas

If the United States biopharmaceutical industry is to continue to grow and expand, companies must be able to attract, train, and retain a highly skilled scientific and technical workforce. While on-the-job training will always be an essential tool for developing the workforce, there is a need

for innovative approaches to prepare students for work in an industrial environment and to provide education and training in new and innovative manufacturing techniques in biopharmaceuticals. These solutions will ultimately serve the industry by:

1) **Growing** the pipeline of new graduates entering the workforce,
2) **Developing** the skills of incumbent workers (scientific, technical, and professional), and
3) **Providing** job retraining to skilled but unemployed (or underemployed) individuals.

Informed by preliminary workforce surveys, presentations from NIIMBL member companies, and teaming meeting discussions, what follows are strategies and topics of interest to NIIMBL to attract, train, and grow the talent pipeline as well as develop, expand, and retrain the highly-skilled scientific and technical incumbent workforce in the United States biopharmaceutical industry.

9.2.1 Strategies of Interest

1. *Academic curriculum & education*

   Develop new academic course modules, courses, "capstone" experiences, and/or programs at the community college, undergraduate, and graduate level.

2. *Incumbent worker curriculum & training*

   Develop short courses, certificate programs, e-learning, or other learning solutions for training incumbent workers.

3. *Internship programs*

   Develop innovative solutions that expand internship and co-op opportunities for students as well as make establishing internship programs easier for SME companies.

4. *Program articulation*

   Develop strategic partnerships between Associate in Applied Science (AAS) programs and BS programs to enhance articulation.

5. *Biopharmaceutical manufacturing case competitions*

   Develop project-based learning opportunities for undergraduate or graduate students based on real-world cases suggested by industry sponsors.

6. *Faculty "sabbaticals" in industry*

   Develop mechanisms for university and/or community college faculty to gain first-hand knowledge of industry through short-duration and immersive shadowing experiences.

7. *Innovative learning solutions*

   Leverage new and emerging training and education tools in curriculum development (digital learning tools, online courses, videos, podcasts, animations, virtual reality, augmented reality) as well as hands-on experiences.

8. *Reaching new and underrepresented populations*

   Develop strategies to attract women, minorities, and veterans, and other underrepresented populations to biomanufacturing-related careers as well as students coming from non-traditional majors such as computer science, electrical engineering, and materials science.

9.2.2 Topics of Interest

1. *Biologics manufacturing*

   Unit operations, regulatory, quality, and foundational science supporting manufacture of antibodies, proteins, vaccines, and other existing products.

2. *Cell therapy, gene therapy, and other emerging products*

   Unit operations, regulatory, quality, and foundational science supporting manufacture of cell therapies (autologous and allogeneic), gene therapies (viral vectors based systems, e.g. AAV), microvesicles and exosomes, and other emerging product modalities.

3. *Emerging manufacturing technologies*

   Examples include: disposable technologies, continuous manufacturing, cryopreservation, and lyophilization (See Technical Project Topic list for additional areas).

4. *cGMP, quality systems, and regulatory affairs*

   Working in a regulated environment (e.g. knowledge of or ability to apply GMP regulations to the workplace), Deviations/Investigations, and change management.

5. *Process control, automation, and data analysis*

   Quality by Design (QbD), Design of Experiments (DoE), adaptive process control, multivariate data analysis, and industrial automation systems.

6. *Professional skills*

   Biomanufacturing industry-relevant education and training in topics such as critical thinking, troubleshooting, communication, technical writing, Lean/Six Sigma, commercialization, project management, and financial management.

7. *Biomanufacturing fundamentals, role/function specific topics*

   Topics include (but not limited to) operations (maintenance, aseptic operations, instrumentation, automation), process development, manufacturing science, quality control/analytical technologies, quality assurance, quality systems, and regulatory affairs. Sufficiently deep understanding of bioprocess fundamentals to make rational decisions in problem solving.

For questions related to this Request for Proposal, please contact projectcalls@niimbl.org.