The National Institute for Innovation in Manufacturing Biopharmaceuticals

Project Call 2.2T
Request for Proposals

Concept Papers due: January 10, 2019

Full Proposals due: May 9, 2019

VERSION November 30, 2018

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 2.2 with member-driven and industry-led priority topic areas for technical and workforce development projects. Tis document contains information for technical projects. For information on workforce projects, please reference Project Call 2.2W.

Funding Opportunity Title: Project Call 2.2T (Technical)

Stage 1: The Concept Phase includes the submission of a 4-page Concept Paper. 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, January 10, 2019**. Submissions received after the deadline will not be considered.

Following submission of Concept Papers, invitations will be issued to participate in the Project Call 2.2 Summit, where proposers will have multiple opportunities to network and discuss their project during a short rapid-fire presentation and an open poster session. This Phase concludes with invitations issued to submit a full proposal in Stage 2 of the process.

Stage 2: 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, May 9, 2019**. Submissions received after the deadline will not be considered.

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

EVENT	DATE
RFP Release	November 30, 2018
RFP FAQ Webinars	December 5, 2018
Concept Paper Due	January 10, 2019
Invite to Project Call 2.2 Summit	Anticipated the week of January 14, 2019
Project Call 2.2 Summit	Anticipated the week of February 18, 2019
Invite for Full Proposal	Anticipated the week of March 4, 2019
RFP FAQ Webinars	TBD
Full Proposal Due	May 9, 2019
Proposal Review	May 14-28, 2019
Committee Review	May 14-28, 2019
Award Decisions Made	Anticipated June 19, 2019

Funding Opportunity Description:

Further details on project topics are found in Section 6.

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

1. Process Analytical Technologies (PAT)
2. Rapid release of Drug Substance and Drug Product
3. Viral Clearance Technology Development
4. Cell Line Development and Engineering
5. Manufacturing Platforms for Cell Therapy Products
6. Continuous Processing Technology Development – Biologics
7. Scale-down Equipment and Models for Biologics Manufacturing Process Development
8. Improved Drug Product Stability
9. Novel Materials for Biomanufacturing
10. Improved Host Cell Protein Detection/Analysis
11. Novel Methods for Characterization of Live Cell Products
12. Improved Cryopreservation or Cell Preservation Technologies
13. Standardized Data Structures

Total Amount to be Awarded: NIIMBL will make available up to $4,500,000 to fund proposals submitted in response to both the PC2.2T and PC2.2W request for proposals, subject to GC approval.

2. Project Requirements and Eligibility Criteria

Project Types

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

For Project Call 2.2, two types of proposals are accepted with the following parameters:

1. Small Proposals: Small proposals are a maximum $300,000 of NIIMBL funding and are required to meet a minimum 1:1 (NIIMBL: partners) cost share requirement.
2. Large Proposals: Large proposals are a maximum $600,000 of NIIMBL funding and are required to meet a minimum of 1:1.25 (NIIMBL: partners) cost share requirement.

All committed cost share must be from non-Federal funding sources.

Period of Performance:

Proposals must not exceed 12 months.

Proposer Eligibility:

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

Stage 2: Full Proposal, a lead project proposer AND 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 **5:00pm Eastern Time on Monday, April 29, 2019.** Information on how to join NIIMBL is available at www.niimbl.org.

Cost Share

There is no requirement to have cost share documented or planned at the Concept Phase. 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 G). Project proposal teams must contact the appropriate State organization for additional information:

Delaware: Contact Marta Rosario (martar@udel.edu) by 5:00 p.m. on April 25, 2019 to request state cost share. The request should include a 1-paragraph description of the project, partners, and budget narrative.

Massachusetts: Massachusetts applicants should submit a draft application to NIIMBLMA@masslifesciences.com by April 24, 2019. Applicants may need to present their proposal in person to the Massachusetts Life Science Center the week of April 29, 2019.

North Carolina: Contact Jon Horowitz (jmhorowi@ncsu.edu) at the NC State Office of Research and Innovation. Requests need to reach this office by 5:00 p.m. on March 1, 2019.

Teaming

There is no requirement to have any partners identified during the Concept Phase. A goal of the Project Call 2.2 Summit is to help concept proposers connect with industry members (across all tier levels), and other NIIMBL members to identify partners and cost share opportunities.

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. Federal employees may also request invitations to the Project Call 2.2 Summit to determine if participation in specific NIIMBL projects would be beneficial. 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 Information on NIIMBL Project Call 2.2 for Federal Stakeholders 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:
https://niimbl.org/Downloads/PC2_2_Guide_HumanSubjects.pdf

Vertebrate Animal Activities

If proposing activities with vertebrate animals, all activities must comply with the Laboratory Animal Welfare Act of 1966 (as implemented in 9 C.F.R. Parts 1, 2 and 3), and all other applicable statutes pertaining to the care, handling, and treatment of warm-blooded animals held for research, teaching, or other activities. Additional guidance related to activities involving vertebrate animals is available:
https://niimbl.org/Downloads/PC2_2_Guide_VertebrateAnimalActivities.pdf

3. Proposal Instructions

3.1 General Instructions

Submissions

Stage 1: Concept Paper 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, January 10, 2019**. Submissions received after the deadline will not be considered.

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, May 9, 2019**. 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 "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 before a panel of reviewers comprised of industry representatives and Federal stakeholders. Proposers first present their concepts in the written form of a Concept Paper. Following this submission, NIIMBL will host the Project Call 2.2 Summit, where invited proposers will have multiple opportunities to network and discuss their project during a brief rapid-fire presentation and a poster session. This Phase concludes with invitations issued 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, 11-point Arial font (or larger equivalent font) and a maximum of 4 pages; via the NIIMBL Proposal Submission Hub by Thursday, January 10, 2019.

The Concept Paper must include:

1. Submitter name and organization
2. Concept title
3. Topic area to be addressed
4. Identified project team partners or desired project team partners and expertise (if known)
5. Background and significance of the problem to be solved
6. Current state of the art; short summary of existing solutions to solve the problem
7. Description of the proposed concept
8. MRL of the proposed concept and short justification
9. 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 MRL transition

	Submission	**Constraints**
Concept Paper	January 10, 2019, via NIIMBL Proposal Submission Hub	Single-spaced 11-point Arial font (or equivalent) Maximum of 4 pages File Type: .pdf only

Project Call 2.2 Summit

The Project Call 2.2 Summit is designed to provide proposers an opportunity to share their concepts with the community for review and evaluation purposes and to provide proposers an additional venue to form teams. Due to practical considerations for engagement from industrial partners, NIIMBL expects to invite no more than 100 concepts to participate in the Project Call 2.2 Summit. All concepts will be reviewed to ensure alignment with the NIIMBL mission (see Section 1), suitability of work within the MRL 4-7 space, and industry interest. Following this review, invitations will be issued during the week of January 14, 2019 to participate in the Project Call 2.2 Summit. Only concepts that have been invited will be eligible to participate in the Summit.

Upon receiving an invitation to present at the Project Call 2.2 Summit, proposers will be required to prepare two additional documents that will be used during the Project Call 2.2 Summit: a slide deck to be displayed during the proposer's brief presentation, and a poster. Proposers will be required to submit their concept slides prior to the Summit, but will not be required to submit their poster to NIIMBL in advance. Note: though the slides and poster are "NIIMBL Confidential," teams should be aware that the presentation will be to an in-person and remote, limited audience of NIIMBL members and Federal stakeholders.

	Submitted upon receiving invitation	Constraints
Concept Slides	Via NIIMBL Proposal Submission Hub	Rapid-fire presentation Marked "NIIMBL Confidential" File Type: .ppt, .pptx only
Concept Poster	Not submitted to NIIMBL in advance of Summit	48" x 36" horizontal orientation

Each proposer is expected to attend the Project Call 2.2 Summit in person, although exceptions to in-person attendance may be considered on a case-by-case basis. During the Project Call 2.2 Summit, submitters will have an opportunity to present their ideas directly to the industry panel and Federal representatives by delivering a brief oral presentation and by participating in an extended poster session. The Project Call 2.2 Summit will likely be scheduled during the week of February 18. More detailed information will be forthcoming.

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) (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
Appendix C	Project Plan (includes Work Breakdown Structure, Responsibilities Assignment Matrix, and Gantt Chart)
Appendix D	Individual Organization Budgets

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

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

A proposal completion checklist can be found at:
http://www.niimbl.org/Downloads/PC2_2_Guide_ProposalChecklist.pdf

Project Partner Information Form(s)

Each unique project organization on the project proposal team must submit a Project Partner Information Form. If your organization is a Federal agency or is a participant in the Federal Demonstration Partnership (FDP) Clearinghouse, your organization may instead elect to submit a Subrecipient Letter of Intent. If your organization is not a Federal agency or a member of the FDP, your organization is required to complete and submit the Project Partner Information Form. All project proposal team organizations must be NIIMBL members or a Federal entity.
https://niimbl.org/Downloads/NIIMBL_Project_Partner_Information_Form_FINAL_112018.pdf

Abstract

The abstract includes the names and information of the lead organization, each partner organization, the PI, all co-PIs, and a brief description of the proposal. 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.

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 MRL level, and the projected impact of the project. The Executive Summary is limited to one page.

Proposal Narrative

The proposal narrative must be single-spaced, 11-point Arial font (or larger equivalent font). The proposal narrative must include all the sections described below and must not exceed 14 pages.

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 MRLs 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, milestones, deliverables, and go/no-go decision points. Describe the success criteria for the project, including metrics for measuring project success. Milestones 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. Examples 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. 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 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: https://www.nsf.gov/pubs/policydocs/pappg17_1/pappg_2.jsp#IIC2f]

Appendix B: **Quad Chart**

Complete a quad chart providing an overview of the proposal's methodology and approach, highlights from the work breakdown structure, the impact, team composition, and budget information. The quad chart is limited to one page and must be submitted as a .ppt or .pptx file. The NIIMBL template is available at: https://niimbl.org/Downloads/PC2_2_Template_AppendixB_ProposalQuadChart.pptx

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 WBS is required for each project proposal team and must include all proposed work. The WBS must be submitted as a .doc or .docx file. A template is available for download at: http://www.niimbl.org/Downloads/PC2_2_Template_AppendixC_ProjectPlan.docx

Appendix D: **Individual Organization Budget**

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

Additional Proposal Appendices

Appendix E: **References**

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

Appendix F: **List of Acronyms**

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

Appendix G: **Commitment Letters**

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

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

If a Tier 3 Industry Member is not a proposed project partner, then a required explanation must have 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: https://niimbl.org/Downloads/PC2_2_Template_AppendixH_T3ExemptionRequest.docx

4. Proposal Review and Evaluation

4.1 Stage I: Concept Paper Evaluation Criteria

NIIMBL Acceptance Criteria

Concept Papers must comply with information requirements outlined in this RFP. Any pages beyond the 4-page limit will be removed before distribution to the review panel. All administrative requirements, terms and conditions, and other appropriate disclosures will be assessed for compliance with this RFP.

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

Concept Paper Presentation - The Project Call 2.2 Summit

No more than 100 concept proposers will be invited to participate in the Project Call 2.2 Summit. If more than 100 concept Papers are received that comply with the information outlined in this RFP, NIIMBL will review concept Papers to ensure alignment with the NIIMBL mission (see Section 1), suitability of work within the MRL 4-7 space, and industry interest. Following this review, invitations will be issued during the week of January 14, 2019 to participate in the Project Call 2.2 Summit. Only concepts that have been invited will be eligible to participate in the Summit.

Concept presentations will be made to a panel of NIIMBL industry members and Federal stakeholders. The NIIMBL industry members will evaluate proposed concepts for the purpose of inviting a full proposal submission, with consideration of the total available funding ceiling.

For technical projects, the Concept Phase evaluation criteria are:

1. The Concept Paper ability to address the topic's problem statement and a relevant industrial need

2. The Concept Paper's demonstration of awareness of existing solutions
3. The Concept Paper's ability to provide a clear value proposition for the project team, the broader NIIMBL community, and/or the biopharmaceutical manufacturing industry
4. The MRL of the concept falling within the NIIMBL mission space

4.2 Stage II: Full Proposal Evaluation Criteria

NIIMBL Acceptance Criteria

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.

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

1. The proposal's ability to provide a solution to an industrial need
2. The proposed solution's difference than or complementarity to existing solutions or related initiatives
3. The speed with which the benefits of the project be realized
4. 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%

5. The merit of the technical approach
6. Whether the project deliverables and timelines are realistic
7. The project's clarity of criteria for success
8. 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:

1. The proposal's ability to provide a solution to an industrial need
2. Whether the technical approach and project plan are likely to result in success
3. The proposal's ability to provide a benefit to NIIMBL members
4. Whether the project complements the existing NIIMBL technology portfolio

5. Whether the initial/final MRL falls within the NIIMBL mission space

NIIMBL Governing Committee

The NIIMBL Governing Committee will take into account the total Project Call 2.2 funding that is available and perform a strategic review of the proposals. The GC will consider the following:

1. Benefit to NIIMBL members
2. NIIMBL sustainability
3. Complementarity to existing NIIMBL project portfolio
4. Cost and scope alignment with proposed benefits
5. Cost share commitment
6. Industry involvement

5. Reporting

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

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

6. Project Call 2.2 Topics

Project Call 2.2 topics areas were informed by NIIMBL's Technology Activities Committee industry members. To the extent that collaboration with Federal Organizations, National Laboratories, or Federally Funded Research and Development Centers (FFRDCs) is appropriate for the success of a proposed project, consider options to include these individuals or organizations. Asterisks indicate Tier 1 industry members listing a project topic area as high priority.

1. Process Analytical Technologies (PAT) ***

Develop novel process analytical technologies (PAT) that provide manufacturers of both biologics and cell and gene therapies with in-line, on-line, or at-line measurements of important process parameters, critical quality attributes and process and product impurities. Sensors that can be applied to speed up current processes and enable future intensified (connected) or continuous processes are of interest to manufacturers. Single-use, robust

sensors that do not require calibration are needed in both drug substance and drug product applications, especially for pH, temperature, dissolved oxygen, CO2, and sensors for metabolites. In-line monitoring combined with multivariate analysis (MVA) will enable feedback/feed-forward methods to control critical quality attributes of the product. Single use sensors for pH, etc., near infrared (NIR) spectroscopy, Raman spectroscopy and mass spectrometry-based methods are among the technologies that would be of interest to apply to in-line, on-line or at-line. There is also promise in the use of Raman spectroscopy to determine protein titer for cell culture media screening, and for use in a scale-down model such as ambr® that is independent of scale and media. Manufacturers would benefit from development of real-time (at-line or in-line) analytical technologies for rapid measurement of protein or mAb sequence variants in bioreactors. 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. Also of interest are PAT projects in process platforms related to flexible manufacturing of biologics that refer to regulatory guidance documents to mitigate risks in using pooled CQA data and QbD knowledge from member companies.

2. Rapid Release of Drug Substance and Drug Product **

Analytical testing currently causes significant delays due to the time it takes to complete the complex and comprehensive characterization needed to ensure raw material quality as well as product identity, purity, and potency. Current compendial methods used for adventitious agents (AA) are time-consuming, with culture-based testing taking up to 28 days. Industry needs include faster detection of microbial, mycoplasma, and/or viral contaminants, and faster and more sensitive methods for endotoxin detection. There are opportunities for aseptic sampling approaches for microbial determination, potentially using clarification. These methods could be applied to final product testing or testing in process, with an overall goal to have results available within 24-48 hours. New approaches could involve molecular methods (e.g., NGS, qPCR) for detecting viral nucleic acids. The focus should be on validation of AA testing methods and providing a framework for demonstrating equivalence to regulators. Projects that reference regulatory guidance in determining potential issues during implementation of these rapid AA technologies are particularly welcome. Highly robust systems for small-volume, non-invasive automatic, sub-visible particle detection are needed to reduce the number of false rejects. Manufacturers are interested in a general over-arching solution to the problem of Low Endotoxin Recovery (LER) which has wide applicability to a broad range of biologic products, including proteins, monoclonal antibodies, vaccines, and cell and gene therapy products.

3. Viral Clearance Technology Development *

There is an unmet need for new unit operations for clearance of viral contaminants. Downstream viral clearance operations are critically important for ensuring adventitious agent control in biomanufacturing of protein and mAb therapeutics. These unit operations are not compatible with continuous manufacturing operations. In-line virus removal validation strategies for connected / integrated processes are needed. Particular interest should be placed on projects that involve novel viral clearance approaches using platform

processes. Novel membranes or monoliths that can remove viruses but do not result in product yield losses would enable such operations. There is a need for standardized, purified, high titer virus challenges that can help establish the required 5 LRV for virus removal, and to establish protocols for measurement and characterization that are aligned with regulatory guidance. Novel assays for DNA / virus removal would also be of great interest.

4. Cell Line Development and Engineering *

Develop novel cell lines, either CHO-derived lines or other alternative platforms, that have increased productivity and/or improved manufacturability to decrease cost of goods for recombinant protein and mAb biotherapeutic products. These new cell lines will enable manufacturers to increase titers, produce more effective and/or safer therapeutics or reduce production times in existing processes. Additionally, these new cell lines may enable the use of lower cost media, processes, and/or equipment that are not currently compatible with mammalian cell cultures. Potential areas of focus could include (but are not limited to) streamlining cell line engineering and cell line development workflows; monitoring cellular metabolism or improving metabolic efficiency to streamline media and feed development; developing novel hosts demonstrating higher productivity or growth; improving critical quality attributes or making them more reproducible; and reducing downstream processing needs. In addition, proposals directed toward developing cell lines specifically for intensified or continuous CHO cell culture or viral vaccine development are of interest to this focus area.

5. Manufacturing Platforms for Cell Therapy Products *

Manufacturers are interested in the development of both custom bioreactors as well as scale-down models for allogeneic operation. Rather than rely on existing platforms for cell growth, it is important to design scaffolds and bioreactors that meet the specific needs of cell therapy manufacturers and facilitate in-process measurements and process control. Manufacturers are also interested in automated RNA and DNA extraction devices for online nucleic acid measurements of cultured cells in a bioreactor. Custom bioreactors capable of culturing 5-50 x 106 cells/ml for T-cell manipulations (selection, activation, transduction) with low shear stress, high mass transfer capability, pH and O2 control, closed loop control and integrated on-line, in-line sensors for measuring metabolites and for performing cell characterization are needed. Alternative, low cost reagents for growth factors, cytokines along with novel growth factor delivery modalities with extended release are of interest for cell therapy manufacturing processes. 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 fill (0.25-10 ml) and at high concentration (15-30x106 cells/ml). It is of interest to identify and chemically synthesize small, inexpensive molecules such as peptides that can bind to T cell receptors and illicit signals similar to those of growth factors that are made using

recombinant methods and are therefore more expensive. There is also interest in solid phase growth factor delivery vehicles in bioreactors that can provide more control and longer exposure to cells and can drive down cost of goods.

6. Continuous Processing Technology Development – Biologics *

High volume biopharmaceuticals made in very large batches to handle the needs for large dosages and / or large patient populations are potential candidates for conversion from single-batch processes to continuous or connected processes. Test bed platforms are needed as a "safe place" to analyze modular, connected or fully continuous manufacturing of biologics. These test beds would be used for training, introducing novel on-line or in-line sensors for process measurement and control, and testing new equipment for continuous or semi-continuous manufacturing. In addition, these platform processes could be used for risk assessment. For instance, testing concepts for adventitious agent removal and monitoring, achieving specific residence time distributions and holds, and demonstrating regulatory approaches to batch validation. Continuous or semi-continuous processes will rely greatly on process modeling, control and automation for proper operation and these test beds would offer an ideal environment for the development of such systems. This effort would be greatly enhanced by collaboration with regulatory scientists on process monitoring and CQA measurements to facilitate and de-risk process validation and batch release. In addition to test beds, manufacturers need novel in-line methods to determine the metabolic state of cells in a continuous or semi-continuous process and strategies for optimizing media / nutrient feed protocols specifically designed for these operations.

7. Scale-down Equipment and Models for Biologics Manufacturing Process Development **

Develop improved scale-down models for the entire biologics platform process (bioreactor, chromatography, filtration, drug product formulation) to enable more rapid and cost-effective process development. Biopharmaceutical manufacturers rely on scale-down models of the manufacturing process as a risk mitigation strategy to determine the impact of operating variables on process performance and product quality. Scaling of aeration and fluid hydrodynamics over a wide range is a challenge, and advancements in computational fluid dynamics (CFD) tools and techniques are needed to help analyze and predict performance. Automated, improved scale-down models with high-throughput testing capability and predictive modeling for the entire process are required. The modeling efforts could also result in improved scale-up protocols for manufacturing. The scaled down models would include all features that are important in the full-scale reactor, including mass transfer, shear effects, temperature, heat transfer, and agitation. Even though there are commercially available automated scale-down models for bioreactors that can be used for testing media and other process conditions, there are difficulties in scaling these to pilot plant or production levels. There are high throughput screening approaches for chromatography but they also are not fully scalable. Less common are scale-down approaches for high-throughput screening of filtration or product formulation processes. Development of these scale-down devices necessarily requires novel sensor technologies able to track process variables. Multivariate analysis (MVA) driven models or mechanistic

models of these devices make them suitable for industrial use. The data obtained from the scale-down models would be extremely useful in developing mechanistic models of the process. Mechanistic models of bioprocess unit operations allow manufacturers to define the appropriate design space and operating ranges for their processes, in contrast to factorial design models. Modeling of unit operations for design of new processes (e.g. continuous / semi-continuous) is one key application. Such mechanistic models can guide scale-down high-throughput approaches to accelerate screening of operating variables, as well as scale-up efforts from the laboratory to pilot scale and beyond. There is also a great deal of interest in scale down models applied to viral vector production to inform scale up and scale out of gene therapies and cell therapies. Scale down model applications for perfusion processes is also an important new application for these systems.

8. Improved Drug Product Stability **

It is important to develop novel approaches to improving the stability of drug products to improve shelf life and potentially to eliminate cold-chain supply issues. This can be done via the use of molecular modeling to influence drug design and address drug stability issues, and improved technologies for drying or lyophilization. These computational and experimental tools could inform molecular design to reduce aggregation and immunogenicity of drug product. It is also important to understand excipient interactions with biologics and their impact on the properties of a formulation, including shelf life, solution phase behavior and stability. Manufacturers need approaches for correlating microscopic or molecular properties with solution phase behavior and product stability during drying and storage. A major challenge is the development of novel cryopreservation agents for CAR T-Cell therapies that are not based on DMSO. The scale up or scale-out of viral vector cryopreservation process is also an important area for gene and cell therapy manufacturing.

9. Novel Materials for Biomanufacturing **

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

standardization of universal connector designs. Such standardization would be enabled via potential collaborations with NIST and other agencies.

10. Improved Host Cell Protein Detection/Analysis *

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.

11. Novel Methods for Characterization of Live Cell Products *

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 the 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. Analytical methods should ideally be non-invasive, label-free, involve small sample volumes, high-throughput and be sensitive enough to distinguish between single cell vs. population. There is need for surrogate and appropriate reference materials.

12. Improved Cryopreservation or Cell Preservation Technologies *

Develop alternatives to 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 operations, as well as requiring strict freezing protocols, and also has compatibility issues with some container types. More dramatic changes to cell preservation technology, such as room temperature storage or cell product spray drying or lyophilization would also be of interest. Manufacturers have interest in excipient selection to promote shelf stability and stability during freeze thaw. There is a need for prefilled syringes that are freezing compatible and other clinically convenient storage and administration devices. There is interest in controlled thawing equipment and understanding the mechanisms of cell instability during freeze thaw.

13. Standardized Data Structures *

Develop a standardized data structure to enable communications between manufacturers, CDMOs, and regulators to facilitate data sharing and filing of license applications. Data structure also plays a key role in enabling the development of mechanistic and statistical models for processes. 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 that contain data from multiple sources. It could also facilitate process and product understanding and potentially improve process control and product quality.

7. List of Acronyms

1. GC: Governing Committee
2. RFP: Request for Proposals
3. FAQ: Frequently Asked Questions
4. FFRDC: Federally Funded Research and Development Centers
5. MRL: Manufacturing Readiness Level
6. WBS: Work Breakdown Structure
7. PI: Principal Investigator
8. Co-PI: Co-Principal Investigator
9. NIIMBL: National Institute for Innovation in Manufacturing Biopharmaceuticals
10. PC2.2T: Project Call 2.2 Technical
11. PC2.2W: Project Call 2.2 Workforce
12. CDMO: Contract Development and Manufacturing Organization
13. qPCR: Quantitative Polymerase Chain Reaction
14. NGS: Next Generation Sequencing
15. NIR: Near Infrared
16. LRV: Log_{10} Reduction Value
17. LER: Low Endotoxin Recovery
18. QbD: Quality by Design
19. RNA: Ribonucleic Acid
20. DNA: Deoxyribonucleic Acid
21. AA: Adventitious Agent
22. CQA: Critical Quality Attribute
23. CFD: Computational Fluid Dynamics
24. MVA: Multivariate Analysis
25. DMSO: Dimethyl Sulfoxide
26. mAb: Monoclonal Antibody
27. HCP: Host Cell Protein
28. CAR: Chimeric Antigen Receptor