



The National Institute for Innovation in Manufacturing Biopharmaceuticals

Project Call 3.1G

Request for Proposals

Concept Papers due: September 10, 2019

Full Proposals due: February 13, 2020

VERSION June 26, 2019



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1. Executive Summary

The NIIMBL Global Health Fund (GHF) was established by NIIMBL with funding contributed by the Bill & Melinda Gates Foundation (BMGF) to develop and implement innovative technologies for vaccine and biological manufacturing that will accelerate development timelines, lower the cost of manufacturing, secure supply for GAVI, the Global Alliance for Vaccines and Immunization, and to ensure appropriate product profiles for their geographies, all in furtherance of BMGF’s charitable objectives (the “Purpose”). To advance the Purpose, BMGF conducted a survey of the members of the Developing Country Vaccine Manufacturers Network (DCVMN) to identify topics that were of greatest interest. The survey revealed that 100% of respondents were interested in the development of alternative *in vitro* assays to reduce the reliance on animal testing required for lot release. Key issues for the DCVMN associated with animal testing include: variability across labs, supply of animal, lack of trained operators, environmental variants and differences in requirements among pertinent regulatory bodies, and the fact that the studies themselves are generally expensive and time consuming. The Bill & Melinda Gates Foundation does not control the selection of the recipient of the award. The Bill & Melinda Gates Foundation will not be a party to the funding agreement, if awarded. The award (if made) will be controlled, made and managed solely by NIIMBL.

Background information from Workshop presentations can be found via the following link:
<https://niimbl.force.com/s/4-18-19-Global-Health-Fund-Workshop>

Funding Opportunity Title: Project Call 3.1G (Global Health Fund)

Stage 1: The Concept Phase includes the submission of a 4-page Concept Paper and a single overview slide. 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 **Tuesday, September 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 3.1 Summit, where proposers will have multiple opportunities to network and discuss their project. 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, February 13, 2020**. Submissions received after the deadline will not be considered. Submissions received that were not invited will not be considered.

This Phase concludes with a decision to fund or not fund the proposal by the GHF Steering Committee.

EVENT	DATE
RFP Release	June 26, 2019
Concept Paper Due	September 10, 2019
Project Call 3.1 Summit	Tentatively scheduled for October 23-24, 2019
Invite for Full Proposal	Late November 2019
Full Proposal Due	February 13, 2020
Proposal Review	Late March 2020
Award Decisions Made	Mid-April 2020



Funding Opportunity Description

Further details on project topics are found in Section 6.

PC3.1 Global Health Fund (GHF) projects are expected to reduce the reliance on animal testing to enhance the ability of manufacture vaccines to, among other things, serve low- and lower-middle income countries. The following project concepts have been defined:

1. Replace animal based adventitious agent testing
2. Create a series of tools to support novel *in vitro* adventitious agent test
3. Identify new *in vitro* release tests to replace animal-based release tests in vaccine manufacturing quality control
4. Address the shortage of suitable reagents for existing legacy vaccines

It is recognized that this is a broad area so proposals will likely focus on a sub set of these opportunities

Total Amount to be Awarded

NIIMBL will make available up to \$1,500,000 to fund proposals submitted in response to PC3.1G request for proposals, subject to GHF Steering Committee approval. It is anticipated that three projects will be funded.

2. Project Requirements and Eligibility Criteria

Project Types

Global Health Fund projects are designed to support advancements of global health related to biopharmaceutical manufacturing. Unlike projects funded by other NIIMBL RFPs (including PC3.1T and PC3.1W), projects funded by PC3.1G are expected to be managed in such a way as to ensure the broadest possible access to those most in need. See section below on Global Access Commitment; IP and Publication for more information. Partner Specific projects as defined in the NIIMBL Bylaws are not an option for PC3.1G proposals. In addition, Global Health Fund project proposals shall be within Manufacturing Readiness Level 4-7. More information on Manufacturing Readiness Level can be found at: <http://www.niimbl.org/project-call-3-1>

Period of Performance

Proposals must not exceed 18 months.

Proposer Eligibility

Stage 1: Unlike other NIIMBL project calls, NIIMBL members, non-members, and Federal employees are permitted to submit concept papers in response to PC3.1G. Note that only NIIMBL members or Federal employees are permitted to submit concept papers in response to PC3.1T and PC3.1W.

Stage 2: To participate on a project proposal team, the lead project proposer AND all members of the proposed project team must be a NIIMBL member or a Federal employee. To be considered a NIIMBL member, an organization must be a member or have submitted a partially-executed NIIMBL Membership Agreement by **5:00pm Eastern Time on Thursday, February 6, 2020**. Information on how to join NIIMBL is available at <https://niimbl.force.com/s/membership-information>.



Budget

Project teams are required to meet a minimum 1:1 (NIIMBL:partners) cost share requirement.

Indirect cost recovery is limited for proposals submitted in response to PC3.1G. See Section 3.3 for more information

Cost Share

All committed cost share must be from non-Federal funding sources. 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 January 10, 2020 to request state cost share. The request should include a 1-paragraph description of the project, partners, and budget narrative.

Massachusetts: Massachusetts applicants planning to submit a full proposal and requesting cost-share from the Massachusetts Life Sciences Center should reach out to NIIMBLMA@masslifesciences.com early in the application process to confirm requirements and dates. MA applicants will be required to submit a draft application to NIIMBLMA@masslifesciences.com the week of January 20, 2020. Applicants may need to present their proposal in person to the Massachusetts Life Science Center the week of January 27, 2020.

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 January 10, 2020.



Teaming

There is no requirement to have any partners identified during the Concept Phase. A goal of the Project Call 3.1 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 3.1 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 PC3.1 Guide [Information for Federal Stakeholders](http://www.niimbl.org/project-call-3-1) available at: <http://www.niimbl.org/project-call-3-1>

Human Subjects Activities

If proposing activities with human subjects, all activities involving human subjects must satisfy the requirements of the Common Rule for the Protection of Human Subjects, as provided for by the Department of Health and Human Services in 45 C.F.R. Part 46 and codified by the Department of Commerce in 15 C.F.R. Part 27. The Common Rule, and the institutional policies that enforce its requirements in activities involving human subjects, exist to ensure adequate protection of human subjects. Additional guidance related to activities involving human subjects is available at: <http://www.niimbl.org/project-call-3-1>

Vertebrate Animal Activities

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



Global Access Commitment; IP and Publication

Global Access Commitment

All projects shall be conducted in a manner that ensures Global Access, and the Global Access commitments will survive the term of the funded project. “Global Access” is a BMGF policy requiring that (a) the knowledge and information gained from the project will be promptly and broadly disseminated; and (b) the Funded Developments will be made available and accessible at an affordable price (i) to people most in need within developing countries, or (ii) in support of the U.S educational system and public libraries, as applicable to the project. “Funded Developments” means the products, services, processes, technologies, materials, software, data, other innovations, and intellectual property resulting from the project (including modifications, improvements, and further developments to Background Technology). “Background Technology” means any and all products, services, processes, technologies, materials, software, data, or other innovations, and intellectual property created by a project participant, or a third party prior to or outside of the project, used as part of the Project.

Humanitarian License

Subject to applicable laws and for the purpose of achieving Global Access, the project participants shall be required to grant NIIMBL and BMGF a nonexclusive, perpetual, irrevocable, worldwide, royalty-free, fully paid up, sublicensable license to make, use, sell, offer to sell, import, distribute, copy, create derivative works, publicly perform, and display Funded Developments and Essential Background Technology. “Essential Background Technology” means Background Technology that is: (a) owned, controlled, or developed by a project participant, or in-licensed with the right to sublicense; and (b) either incorporated into a Funded Development or reasonably required to exercise the license to a Funded Development. Project participants shall be required to certify that they have retained sufficient rights in the Funded Developments and Essential Background Technology to grant this license. The project participants must ensure this license survives the assignment or transfer of Funded Developments or Essential Background Technology. On request, the project participants must promptly make available the Funded Developments and Essential Background Technology to NIIMBL or BMGF for use solely under this license.

Publication

Consistent with the Global Access commitments, if the project description specifies Publication or Publication is otherwise requested by NIIMBL or BMGF, project participants shall be required to seek prompt Publication of any Funded Developments consisting of data and results. “Publication” means publication in a peer-reviewed journal or other method of public dissemination specified in the project description or otherwise approved by NIIMBL and BMGF in writing. Publication may be delayed for a reasonable period for the sole purpose of seeking patent protection, provided the patent application is drafted, filed, and managed in a manner that best furthers Global Access. If project participants seek Publication in a peer-reviewed journal, such Publication shall be under “open access” terms and conditions consistent with the Foundation’s Open Access Policy available at: www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy, which may be modified from time to time. Nothing in this section shall be construed as requiring Publication in contravention of any applicable ethical, legal, or regulatory requirements.

Intellectual Property Reporting

During the term of the project award agreement associated with the funded project, and for five (5) years after, project participants will be required to submit to NIIMBL and BMGF upon request annual intellectual property reports related to the Funded Developments, Background Technology, and any related agreements using NIIMBL’s and/or BMGF’s templates or forms, which may be modified from time to time.



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 **Tuesday, September 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, February 13, 2020**. 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, Federal and BMGF stakeholders. Proposers first present their concepts in the written form of a Concept Paper. Following this submission, NIIMBL will host the Project Call 3.1 Summit, where invited proposers will have the opportunity to present and discuss their concept with other attendees. 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; along with a single PowerPoint slide summarizing the proposed concept and value proposition, via the NIIMBL Proposal Submission Hub by **Tuesday, September 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 the global health market, including expected benefits to people in low- and lower-middle income countries. Considerations include return on investment, time to impact in the industry, and planned MRL transition.

	Submission	Constraints
Concept Paper	September 10, 2019, via NIIMBL Proposal Submission Hub	Single-spaced 11-point Arial font (or equivalent) Maximum of 4 pages File Type: .pdf only
Concept Summary Slide	September 10, 2019, via NIIMBL Proposal Submission Hub	Single-slide Standard size (4:3) File Type: .ppt or .pptx only

Project Call 3.1 Summit

The Project Call 3.1 Summit is for proposers to share their concepts for review and evaluation purposes and to provide an additional opportunity to form teams. Due to practical considerations for engagement from industrial partners, NIIMBL may limit the number of concepts that are invited to participate in the Project Call 3.1 Summit. All concepts will be reviewed to ensure alignment with the intended outcomes of this project call (see Section 1), suitability of work within the MRL 4-7 space, and industry interest. Following this review, invitations to participate in the Project Call 3.1 Summit will be issued. Only concepts that have been invited will be eligible to participate in the Summit.

Upon receiving an invitation to present at the Project Call 3.1 Summit, proposers will be required to prepare a poster. Proposers will not be required to submit their poster to NIIMBL in advance.

	Submitted upon receiving invitation	Constraints
Concept Poster	Not submitted to NIIMBL in advance of Summit	48" x 36" horizontal orientation

Each proposer is expected to attend the Project Call 3.1 Summit in person. The Project Call 3.1 Summit is tentatively scheduled for October 23-24, 2019. More detailed information, including the exact dates, 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), or Letter(s) of Intent (not counted towards the page count)
2. Abstract (200 words max; not counted towards the page count)
3. Executive Summary (up to 1 page; not counted towards the page count)
4. Proposal Narrative (up to 14 pages)
5. Required Proposal Appendices (not counted towards the page count)

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



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/project-call-3-1>

Project Partner Information Form(s)

Each unique project organization on the project proposal team must submit either a Project Partner Information Form or a Letter of Intent. If your organization is a Federal agency or is a participant in the Federal Demonstration Partnership (FDP) Clearinghouse, your organization should submit a Letter of Intent. All other organizations are required to complete and submit the Project Partner Information Form. All project proposal team organizations must be NIIMBL members or a Federal entity. Templates for the Project Partner Information Form and the Letter of Intent are available at: <http://www.niimbl.org/project-call-3-1>

Abstract

The abstract includes the names and information of the lead organization, each partner organization, the PI, all co-PIs, and a brief description of the proposal. This description is limited to 200 words. It will be released to the public if an award is made; therefore, teams are expected to ensure that it does not contain any confidential or proprietary information.

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

Executive Summary

Summarize the proposed work including the technology development objectives and how they are consistent with the Project Call topic area, BMGF alignment, 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 and advance the Purpose defined above.

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, including the Purpose defined above. Describe the overall value proposition and the positive impact on developing countries. 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/pappg19_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: <http://www.niimbl.org/project-call-3-1>



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

The WBS for the proposed project forms the foundation of the proposed project plan. Align the WBS with the Responsibility Assignment Matrix to describe how responsibility will be shared across the identified WBS elements. The Gantt chart will visually show how the work will be completed over time. One Project Plan is required for each project proposal team and must include all proposed work. The Project Plan must be submitted as a .doc or .docx file. A template is available for download at: <http://www.niimbl.org/project-call-3-1>

Appendix D: **Individual Organization Budget**

Provide individual budget workbooks for the lead organization and each of the partner organizations requesting funding and/or committing cost share to the proposed project. Budgets are to be organized by WBS Level 2 Segments. The budget template allows for 5 WBS Level 2 Segments. Any project proposal team with more than 5 WBS Level 2 Segments is asked to email projectcalls@niimbl.org for further direction on how to complete the budget workbook. The budget template is available for download at: <http://www.niimbl.org/project-call-3-1>

Proposals submitted in response to PC3.1G must closely consider the indirect costs (also called Facilities and Administrative Costs) that are included in the Individual Organization Budget. Indirect costs budgeted must adhere to the Indirect Cost Policy of the Bill & Melinda Gates Foundation, which can be found at https://docs.gatesfoundation.org/documents/indirect_cost_policy.pdf, in addition to the federal guidance found at 2 CFR 200.414. The Bill & Melinda Gates Foundation places restrictions on the maximum indirect cost rates that can be charged are driven by the type of institution:

1. Government agencies and other private foundations may not charge indirect costs
2. U.S. universities and community colleges may not charge indirect costs in excess of 10% of total direct costs
3. For-profit organizations, non-governmental organizations, and multilateral organizations may not charge indirect costs in excess of 15% of total direct costs

The federal government requires that an organization have a federally negotiated rate or limit their indirect cost recovery to no more than 10% of modified total direct costs. Project partners are encouraged to carefully review both guidance and determine the appropriate rate to charge that would ensure compliance with both policies. Please email projectcalls@niimbl.org with any questions about how to determine the correct indirect cost rate.

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

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: <http://www.niimbl.org/project-call-3-1>

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 3.1 Summit

NIIMBL will review concept Papers to ensure that they comply with the intended outcomes of this Project Call (see Section 1), suitability of work within the MRL 4-7 space, and industry interest. Following this review, invitations to participate in the Project Call 3.1 Summit will be issued. Only concepts that have been invited will be eligible to participate in the Summit.

A panel of NIIMBL industry members, Federal stakeholders, and BMGF representatives will be selected to review concepts at the Summit. 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 and global health 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, and the global health market
4. The MRL of the concept falling within the NIIMBL mission space

4.2 Stage II: Full Proposal Evaluation Criteria

Proposals that are submitted will follow an evaluation process that relies on subject matter experts, the expertise of the relevant NIIMBL committees, with final selection to be completed by a special GHF Steering Committee with input from both BMGF and NIIMBL members. Final decisions on which subgrantees to award rests with NIIMBL



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 minimum cost share ratio.

NIIMBL Subject Matter Expert Review Panel

GHF 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 an innovative solution to critical global health needs for safe, potent, and readily accessible vaccines for infectious diseases that, among other things, benefit people most in need in developing countries
2. The proposed solution's ability to improve the efficiency of existing testing methods leading to a reduction of testing in animals; especially in situations where the *in vivo* tests are inadequate
3. The speed with which the benefits of the project will be realized
4. The proposal's ability to provide a clear value proposition for the project topic area
5. The proposal's ability to reduce time, costs, resources and accelerate implementation timelines for vaccine production for developing countries vaccine manufacturers (DCVMs).

Technical Assessment – 60%

6. The merit of the technical approach
7. Whether the project deliverables and timelines are realistic
8. The project's clarity of criteria for success – provide a transition pathway to *in vitro* testing, predict key quality attributes necessary for product safety and efficacy
9. The team's inclusion of the needed technical expertise, including project management

GHF Steering Committee (to be chartered by the GC and TAC)

The GHF Steering Committee will perform an impact review using the following criteria:

1. The proposal's ability to provide a solution to critical global health needs for vaccines addressing infectious diseases
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 and people most in need in developing countries
4. Whether the initial/final MRL falls within the NIIMBL mission space (MRL 4-7)

Additionally, the GHF Steering Committee will take into account the total Project Call 3.1 funding that is available and perform a strategic review of the proposals. The Steering Committee will consider the following as well:

1. Benefit to NIIMBL members and the mission of Bill & Melinda Gates Foundation
2. NIIMBL sustainability
3. Cost and scope alignment with proposed benefits
4. Cost share commitment
5. Industry involvement

5. Reporting

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

6. Project Call 3.1 Topics

1. Replace animal based adventitious agent testing

Develop replacement *in vitro* assays for *in vivo* adventitious agent tests for use in vaccine manufacture through application of modern, fast adventitious agent tests. Assays should be developed or have clear development pathway into a format and cost profile that could be appropriate for manufacturing/QC testing of vaccines that benefit people in low/middle-income countries to use. In addition to the development of novel technologies, proposals should address their approach to ensuring that the assay is accepted as a replacement to current *in vitro* methods. Proposals that attempt to correlate between current *in vivo* methods and new *in vitro* methods should specifically account for the known variability of current *in vivo* methods. There is a particular interest in supporting adventitious agent testing in high priority vaccines such as pertussis, rabies, polio and diphtheria.

The results of this effort should include a technical publication of the method developed and guidance and any feedback from a pertinent regulatory authority. The ideal outcome for this effort would be to provide an *in vitro* method suitable for vaccines for L/MIC usage, and results of discussions with a stringent regulatory authority regarding general approaches to acceptance of the new technology.

The following specific test methods are of interest:

- a. *In vivo* neurovirulence test
- b. Specific toxicity
- c. Abnormal toxicity
- d. For the above mentioned *In-Vivo* tests for Adventitious Virus can be plausibly replaced with a well-developed and validated In-vitro assays using as examples, PCR/ Microarrays/Next Generation Sequencing (NGS) / Massively Parallel Sequencing (MPS) / High Throughput Sequencing (HTS) cell culture/ELISA methodology

2. Create a series of tools to support novel *in vitro* adventitious agent test

Develop prototype tools to support novel *in vitro* adventitious agent testing including but not limited to including a combination of reference virus panels, unified bioinformatics data and information, standardized validation protocols, PCR primers and next-generation deep sequencing techniques.

The developed tools should be made broadly available. Specifically encouraged are tools that are fast, inexpensive, robust, novel and transformational. The prototype output of this project should be broadly available for evaluation by global regulatory agencies. Proposals should address how

the tool will be maintained and funded subsequent to the initial investment by NIIMBL to support the tool's development.

3. Identify new *in vitro* release tests to replace animal-based release tests in vaccine manufacturing quality control

Develop new *in vitro* release methods that correlate with critical quality attributes, and have greater precision and accuracy for vaccine QC release methodologies. In many cases it is anticipated that multiple *in vitro* tests will be required to substitute for a single *in vivo* method. Proposals should consider the possibility of multiple *in vitro* tests to replace an *in vivo* method.

An inherent challenge with replacement of *in vivo* assays with *in vitro* assays is the variability of the *in vivo* assay to be replaced. There are a number of examples where efforts of this nature have failed due to this variability. This variability makes a formal correlation of outcome between the *in vivo* assay and replacement *in vitro* assay difficult and sometimes impossible. For detailed information about these challenges, proposers are encouraged to review the European Pharmacopoeia Commission Monograph No. 50214 titled "*In vivo* assay substitution with *in vitro* methods for quality control of vaccines". Proposals should provide their rational and approach to working through these issues.

4. Address the shortage of suitable reagents for existing legacy vaccines

Related to the development of new *in vitro* assays is the availability of reagents to test legacy vaccines. For reagents that are either currently available but in limited supply or for reagents developed in the above section, proposals are requested to develop and implement plans to ensure a sustainable supply of these reagents that are accessible to the global vaccine manufacturing community.

Possible topics include:

For the following products, develop a suitable standard reagent for potency testing.

- Rabies: monoclonal antibodies are required for ELISA testing. Cell lines for PRNT assay
- Polio
- Whole cell pertussis:
 - Availability of coating reagent B. pertussis 18323 and positive control serum
 - Replacement of BET test with MAT (Monocyte activation test): This require cell culture of monocytes MM6 cell line.

Assays developed should leverage available clinical data and clinical samples. The primary outcome of this effort will be the technology transfer of the new reagent to an organization that maintains and distributes a library of global standards with a global access commitment.

The following reagents are of high priority and interest:

- a. Cell bank
- b. Reference antigen
- c. Reference toxin (if needed)
- d. Reference antiserum
- e. Specific primer for amplification
- f. Bioinformatics data of the reference antigen



7. List of Acronyms

1. BET: Bacterial Endotoxins Test
2. Co-PI: Co-Principal Investigator
3. DCVMN: Developing Country Vaccine Manufacturers Network
4. ELISA: Enzyme-linked Immunosorbent Assay
5. FDP: Federal Demonstration Partnership
6. FFRDC: Federally Funded Research and Development Centers
7. GC: Governing Committee
8. GHF: Global Health Fund
9. HTS: High Throughput Sequencing
10. IP: Intellectual Property
11. L/MIC: Low/Middle Income Countries
12. MAT: Monocyte Activation Test
13. MPS: Massively Parallel Sequencing
14. MRL: Manufacturing Readiness Level
15. NGS: Next Generation Sequencing
16. NIIMBL: National Institute for Innovation in Manufacturing Biopharmaceuticals
17. NSF: National Science Foundation
18. PCR: Polymerase Chain Reaction
19. PC3.1G: Project Call 3.1 Global Health Fund
20. PI: Principal Investigator
21. QC: Quality Control
22. RFP: Request for Proposals
23. TAC: Technical Activities Committee
24. WBS: Work Breakdown Structure

8. Release

The Bill & Melinda Gates Foundation assumes no responsibility for costs to respond to this RFP. Applicant agrees not to bring a legal challenge of any kind against the Bill & Melinda Gates Foundation relating to any matter arising from this RFP.

APPENDIX A. Background information for various assays

- For cell bank characterization the following *In vivo* tests are recommended in compendia as these tests detect adventitious agents including many viruses:
- Coxsackievirus types A and B (type B is also detectable in cell culture) and other picornaviruses (e.g., polioviruses and echoviruses), alphaviruses, bunyaviruses (e.g., phleboviruses and nairoviruses), arenaviruses, flaviviruses, rabies, and herpesviruses (e.g., herpes simplex virus). These tests are performed in suckling mice.
- Tests in Guinea pigs is recommended for test detection of Mycobacterium tuberculosis and adventitious viruses including paramyxoviruses (including Sendai virus), reoviruses, and filoviruses.
- Tests in Rabbits is recommended for test detection of simian herpes B virus, and should be considered when primary monkey cells are used.

The table below outlines current safety tests and possible replacements for those tests and also improvements of interest to potency tests:

<i>Safety Tests</i>	<i>Potency tests</i>
<u>All vaccines</u> - Remove of Abnormal toxicity test (removed by EU PH Jan 2019, WHO ECBS Oct 2018)	Diphtheria – Reduce and Refine in vivo challenge with serological potency test. Replacement opportunities to be further explored (Vac2Vac) based on physico- and immunochemical techniques (SSD-PAGE, primary amino group determination, fluorescent spectroscopy, circular dichroism and biosensor analysis) can be used to characterize the diphtheria antigen and identify differences in experimentally produced diphtheria toxoid.
<u>Tetanus containing Vaccines</u> – Replace in vivo absence of toxin and irreversibility of toxoid with BINACLE assay (EDQM BSP136) or with other functional cell-based assays	Tetanus - Reduce and Refine in vivo challenge with serological potency test based on ELISA or ToBI (toxin- or toxoid-binding inhibition) ELISA. Other ELISA and set of physico- and immunochemical methods to be further developed and validated (Vac2Vac).

<p><u>Acellular Pertussis</u> - Replacement of the histamine sensitization test in mice (HIST) by a standardized CHO cell-clustering assay for residual pertussis toxin testing (BSP114 – effective Jan 2020). Remove of final lot testing for residual pertussis toxin, and the deletion of testing for the irreversibility of the pertussis toxoid (Eu PH effective Jan 2020)</p>	<p>Whole-cell pertussis – Reduce and refine in vivo challenge potency assay (Kendrik test) with a serological assay (BSP114).</p>
<p><u>Whole-cell pertussis</u> – Replace the Specific toxicity test – Mouse Weight Gain Test MGWT – with a combined mouse toxicity (LAL) and immunogenicity test (Van Straaten et al. 2002)</p>	<p>Rabies vaccine – Replace and reduce the NIH test with serological tests such as: RFFIT- Rapid Fluorescent Focus Inhibition Test and FAVN – Fluorescent Antibody Virus Neutralization Test. Or alternative based on antigen quantifications: Single Radial Immuno Diffusion Test (SRID), ELISA or Antibody binding test. Replace opportunity with ELISA (BSP148).</p>
<p>Replace the Rabbit Pyrogenicity Test and LAL with Monocyte Activation Test (MAT)</p>	
<p><u>Polio Vaccine</u> – Reduce and refine the neurovirulence test on non-human primates with the use of transgenic mice. Use of MAPREC on bulk before in vivo batch release testing. <u>Oral Polio Vaccine</u> – Replace the neurovirulence test with use of MPS (massive parallel screening) for identify and quantifying mutation profiles (WHO, 2013?)</p>	