Grand Challenge:

Innovations in Vaccine Manufacturing for Global Markets

Contents

The Grand Challenge

"Humanity's greatest advances are not in its discoveries, but in how those discoveries are applied to reduce inequity."

– Bill Gates

Executive Summary

Vaccines are one of the most powerful and effective health interventions ever developed, and also provide tremendous economic and societal value in averted costs, productivity gains, and poverty reduction. Yet a number of factors interact to limit complete global immunization coverage, and among those is the cost of procuring and distributing vaccines in lower income countries. A substantial reduction in the cost of manufacturing vaccines could help enable affordable, equitable and sustainable immunization on a global scale, while also enabling manufacturers to develop sustainable business models around such products. To that end, the Bill & Melinda Gates Foundation is soliciting innovative proposals to develop manufacturing platforms that can transform production economics and produce vaccines at a final finished goods production cost of ≤ $0.15 per dose. The proposed research and development will focus on vaccines that target diseases of great global burden and that are among the most costly to produce with current technologies: human papillomavirus, inactivated poliovirus, measles-rubella, pentavalent, pneumococcal, and rotavirus vaccine. This work is envisioned as a five year, two phase process, in which Phase 1 establishes proof of concept and line of sight to the ≤ $0.15 per dose production cost target, and Phase 2 engages translational partners as needed to optimize and validate the platform for the cost target as well as submit an Investigational New Drug application or equivalent to the appropriate national regulatory agency. Creative approaches are encouraged that are suitable for high volume production, but that achieve cost reduction via meaningful innovation, not simply economies of scale. This Grand Challenge does not define the style of the solution, but is definitive in the impact it seeks: the solution must clearly demonstrate the potential to significantly increase global access to priority vaccines by lowering the manufacturing cost required to produce them.

Background

Despite recent gains in global vaccine coverage, the World Health Organization (WHO) estimates that, in 2013, 21.8 million infants worldwide did not receive complete basic immunizations. Further, of the 5.2 million deaths annually among children under the age of five, nearly one third are preventable by vaccines[1]**.** Incomplete vaccine coverage results from a

[1] WHO "Global Immunization Data" (2014)

number of factors, including limited resources, poor health system management, competing health priorities, and inadequate monitoring. The cost of procuring and distributing vaccines in lower income countries also limits their availability to much of the world's population.

The public-private partnership Gavi, The Vaccine Alliance works to increase immunization coverage in the poorest countries and to accelerate the adoption of new vaccines. Gavi engages UNICEF to procure these vaccines, which in 2014 totaled approximately 490 million doses[2] valued at approximately $1 billion inclusive of procurement costs[3]. Gavi and UNICEF work with manufacturers to secure a reliable supply of vaccines to enable the broadest possible coverage for over 70 of the poorest countries in the world. Because Gavi operates with a fixed budget, innovations that reduce manufacturing cost could enable broader immunization reach with more antigens.

These innovations could also enable long-term sustainability of immunization efforts after Gavi support ends. Countries whose gross national income per capita crosses the Gavi eligibility threshold will start phasing out of Gavi support, absorbing increasing proportions of the vaccine procurement costs until they fully finance vaccine purchasing on their own. A fully sustainable solution for long-term procurement by these poorer countries has not yet been devised. Substantial reduction in vaccine manufacturing cost could be a crucial component in achieving equitable and sustainable immunization on a global scale, especially as an increasing number of unvaccinated children live in countries not eligible for Gavi support.

While a number of vaccines can be produced at very low cost (perhaps the most notable being oral polio vaccine), production costs for more innovative vaccines can be orders of magnitude higher than these older vaccines. Vaccine manufacturing solutions are needed that will dramatically decrease cost, such that manufacturers can offer the vaccines at affordable prices and still engage in a financially sustainable business.

Objectives

The Bill & Melinda Gates Foundation (the foundation) is soliciting proposals to develop manufacturing platforms that can transform vaccine production economics and produce vaccines at a final finished goods production cost of ≤ $0.15 per dose. To ensure the greatest impact in applying discoveries to reduce inequality, the vaccine must come from the below priority list (given in alphabetical order). These vaccines target diseases of great global burden and are among the most costly to produce with current technologies.

- Human papillomavirus vaccine
- Inactivated poliovirus vaccine
- Measles-rubella vaccine
- Pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, Hib)

[2] Gavi, "Global Vaccine Demand Forecast" (2014)
[3] UNICEF SD Annual Report (2014)

- Pneumococcal vaccine
- Rotavirus vaccine

The target production cost of ≤ $0.15 per dose should represent the fully-loaded cost, which ensures that all relevant costs are accounted for. The fully-loaded cost should be inclusive of consumables, direct and indirect labor, facility, equipment and related costs, QA/QC costs, fill-finish, and licensing costs. Any grants or other funding that does not need to be repaid should be deducted from the cost base. Because vaccines are often produced in shared facilities and delivered to multiple markets, allocations of some costs (e.g., by volume) may be used to apportion shared costs and expenses included in the vaccine's fully-loaded cost base.

This Grand Challenge seeks innovative approaches to producing low-cost vaccines with platforms that are suitable for high volume production (i.e., at least 40M doses annually) in order to achieve global impact. It is expected that increased production volume could help enable the target production cost of ≤ $0.15 per dose, however, the core cost reduction should result from meaningful innovation, and not be primarily realized through economies of scale for existing platforms. The proposed solution should also demonstrate cost impact on a much smaller production scale (i.e., 5M doses annually).

This call is open to a wide range of solutions, from incremental process innovation to more disruptive platform innovation. The solution may harness a reconfiguration of existing technology, it may take the form of a brand new technology, or it may fall anywhere on the spectrum between those poles; however, it should be focused on manufacturing and process innovation rather than on target identification. This Grand Challenge does not define the style of the solution, but is definitive in the impact it seeks: the solution must clearly demonstrate the potential to significantly increase global access to priority vaccines by lowering their manufacturing cost.

Applicants are encouraged to consider integrated novel process and analytical strategies that push the boundaries of the standard "process defines the product" paradigm for vaccines, moving closer to a well-characterized paradigm. This work is envisioned in two phases:

Phase 1
Proof of Concept
Years 1-2.
The primary output of Phase 1 will be the development of a platform that can produce a vaccine candidate from the priority list that will meet or exceed the quality standards established for the same vaccine candidate produced through existing technology, as defined by the appropriate national regulatory authority. The platform must be accompanied by an economic model providing line of sight to achieving ≤ $0.15 per dose production cost, but physical demonstration that the manufacturing platform meets specific manufacturing cost targets is not required at this stage. Note that while the platform must only be validated with one priority vaccine, illustrating the process by which this manufacturing platform could be extended to an additional vaccine(s) will also be required to trigger Phase 2 funding. Only if the success criteria from Phase 1 are met will additional funding for Phase 2 be considered.

Phase 2
Development of Economic Viability and Cross-Vaccine Demonstration
Years 3-5.
For projects continuing with Phase 2 funding, the goal is to optimize the validated platform to produce final finished goods vaccine(s) at ≤ $0.15 per dose. This cost should be largely insensitive to scale, down to five million doses (i.e., low production cost should not be achieved primarily through efficiencies gained by increasing production scale). To ensure global impact, the platform should be developed in this phase to allow for annual production capacity of 40 million doses, as demonstrated through feasibility modeling. By the end of year 5, an Investigative New Drug application (INDa) or equivalent must be made to the appropriate national regulatory agency to begin human clinical trial testing of vaccine produced using the new process. The final manufacturing process must be capable of meeting WHO pre-qualification requirements.

This Grand Challenge seeks detailed proposals for Phase 1 of this work, with a higher-level description of plans for Phase 2. It is understood that much of the Phase 2 work will depend on outcomes from Phase 1 that cannot be predicted in advance. Proposers selected to move forward will work closely with the foundation to clearly and specifically define customized milestones that must be met at the end of Phase 1 in order to trigger Phase 2 funding.

While the foundation recognizes that meeting the overall goals will likely require innovations in multiple steps of manufacturing (e.g., bulk manufacturing plus fill-finish plus analytics), proposals will also be accepted for discrete subsets of the objectives laid out here. The foundation will consider strong ideas for work to be done on components of a manufacturing platform, possibly as standalone pieces of work, or the foundation may suggest the grouping of complementary workstreams by multiple partners into a single project.

Requirements

Only proposals that address at least one of the following vaccines in Phase 1 of the work will be considered: human papillomavirus vaccine, inactivated poliovirus vaccine, measles-rubella vaccine, pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, Hib), pneumococcal vaccine, and rotavirus vaccine.

The vaccine(s) selected must be one(s) for which there are established clinical immunogenicity and/or efficacy endpoints for regulatory approval so that a quality comparison may be made between the existing and novel platform technologies.

By the end of year 5 of this project, an INDa or equivalent submission must be made to the appropriate WHO-recognized national regulatory agency. The manufacturing process must be capable of meeting WHO pre-qualification requirements. More information about WHO pre-qualification may be found at: http://www.who.int/topics/prequalification

Award

This Grand Challenge does not specify funding limits or expectations. The number of awards and quantity of each award amount will depend upon the quality of the proposals received. Proposers are expected to develop a budget commensurate with the scope and scale of the work necessary to achieve the objectives laid out therein.

A note on collaboration

Collaboration is a core goal of this project and will be integral to success. It is expected that the project will incorporate work from multiple technical disciplines. Whether these cross-disciplinary partnerships come from research/academic and/or commercial institutions is up to the proposer. The makeup and strength of the team will be evaluated in the initial letter of intent review phase, after which the foundation may offer comments or suggestions. The foundation maintains a strong partner network in vaccines development and manufacturing, and may leverage that network to facilitate collaboration where appropriate and acceptable to potential partners.

Application and Key Terms and Conditions

Schedule

Key Dates*	Event
Thursday, November 5th, 2015 11:30 am U.S. Pacific Standard Time	Letter of Intent (LOI) application deadline
Early January 2016	Notification of invitation to submit full proposal
February 23rd, 2016 11:30 am U.S. Pacific Standard Time	Full proposal application deadline (invited proposals only)
April 2016	Proposal review completed
May 2016	Selections completed and notifications sent

**Note, any changes to these dates will be posted on the Grand Challenges website*

Eligibility

Grand Challenges is open to both foreign and domestic organizations, including non-profit organizations, for-profit companies, international organizations, government agencies and academic institutions. Individuals and organizations classified as individuals for U.S. tax purposes (including sole proprietorships and some single member limited liability companies) are not eligible to receive an award as part of the Grand Challenges initiative from the foundation.

The foundation expects that program goals for this Grand Challenge may be met by applicants intending to perform fundamental research, i.e., basic or applied research, the results of which ordinarily are published and shared broadly within the scientific community and made available consistent with Global Access. If proposals are selected for award that offer a solution other than fundamental research, then the foundation may require the applicant to modify the proposed LOI or proposal to bring the research back into line with fundamental research or otherwise meeting the requirements of the foundation.

How to Apply

LOIs are invited for submission through the foundation's Unison Portal (applicants must first create a log-in for Unison), RFP number SOL1139572.

The application process will require the proposer to agree to the Website Terms of Use and Privacy Policy, and acknowledge that any information provided (either orally or in writing) will be subject to and handled in accordance with such provisions.

This request for proposals will make use of a two-step application process:

Step 1: LOI Submission: Applicants must submit an LOI following the guidelines detailed in the Format section below. Foundation staff, along with external consultants, will evaluate LOIs and the foundation will invite select applicants to submit a full proposal. This invitation may also include feedback and/or specific direction to be incorporated in the full proposal.

Step 2: Invited Full Proposals. Applicants invited to submit a full proposal will receive detailed instructions at the time of the invitation.

Format

LOIs should be designed to communicate the proposer's core objectives and plan. **The total length of the LOI should not exceed 3 pages.** The LOI should address the following elements:

A. Technical goals and rationale. Describe and justify the specific technical objectives to be accomplished in this work.

B. Proposed approach. Succinctly describe the uniqueness and benefits of the proposed approach relative to the current state-of-art alternate approaches. In this section it is important to articulate a logical and compelling narrative framing how the proposed approach will meet the stated production cost objective.

C. Planned deliverables. State the intended output of the research project by phase, with particular focus on the plans for and capabilities in technology transfer and commercialization. Identify intermediate objectives and associated milestones to be met for each phase prior to the end output.

D. Team and organization. A clearly defined organization for the program team which includes, as applicable and possible: (1) the programmatic relationship of each team member; (2) the unique capabilities of team members; (3) the task or responsibilities of team members; and (4) the teaming strategy among the team members.

E. Schedule and cost. Include estimates of cost, by year and by category: personnel, necessary travel, supplies, contracted services, sub-grants, consultants, and equipment. Explain how the schedule and cost map to the proposed approach and planned deliverables.

Allowable Costs

Grant funds may be used for the following costs: personnel, necessary travel, supplies, contracted services, sub-grants, consultants, and equipment. For more detailed information, including allowable indirect costs, please refer to the foundation policy.

Evaluation and Selection Process

The Grand Challenges application review process is executed as follows:

1. Screening of LOI applications to evaluate whether proposals address the fundamental challenge objectives. Applicants with proposals removed from consideration during the screening process will be notified that their proposals were declined but will not receive specific feedback.

2. Reviews are chaired or co-chaired by technical leads from the foundation and other partners, and are conducted by reviewers both outside and within the foundation.

Reviewers are asked to evaluate the LOI, considering its strength along the following dimensions:

A. Overall scientific and technical merit: Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that a final outcome that achieves the goal can be expected as a result of award. The proposal identifies major technical risks and planned mitigation efforts are clearly defined and feasible.

B. Potential contribution and relevance to the foundation mission: The intended output of the project is clearly linked to the mission of the foundation Global Health Division, which aims to harness advances in science and technology to save lives in developing countries. The proposer has carefully considered the foundation's Global Access approach.

C. Level of innovation: The project's approach is creative and clearly differentiated from existing approaches and other applicants.

D. Organizational and investigator capability: The proposed technical team has the expertise and experience to accomplish the proposed tasks, and manage the cost and schedule. The proposal is both thoughtful and thorough in identifying and assembling a highly capable team.

E. Plans and capability to accomplish technology transition: The proposal addresses a plan for technology transfer and commercialization.

3. Validation and final selection of the LOI applicants to be invited to submit full proposals. Invited proposals will be provided additional instructions at that time.
4. Evaluation of the full proposal, with the inclusion of a more detailed review of the project plan and capability to execute the work.
5. Validation and final selection of the proposals to be funded. Proposals selected for funding may be subject to specific modifications which will be negotiated as part of the award process.
6. Due diligence review to ensure that applicants are appropriate recipients of foundation funds and to directly discuss and negotiate any adjustments to the proposed project recommended during the review process. Investigators will be contacted as part of the due diligence review.

To identify and avert conflicts of interest among application reviewers, such reviewers will not be permitted to review proposals from organizations with which the reviewer has self-identified conflicts of interest.

Contact

Please direct all questions about this initiative to: vaccineinnovations@gatesfoundation.org

Disclosure Notice

To help the foundation with its review of responses to this Grand Challenge, the foundation may disclose proposals, documents, communications, and associated materials submitted to the foundation in response to this Grand Challenge (collectively, "Submission Materials") to its employees, contingent workers, consultants, independent subject matter experts, and potential co-funders. Please carefully consider the information included in the Submission Materials. If you (the "Applicant") have any doubts about the wisdom of disclosure of confidential or proprietary information, the foundation recommends you consult with your legal counsel and take any steps you deem necessary to protect your intellectual property. You may wish to consider whether such information is critical for evaluating the submission or if more general, non-confidential information may be adequate as an alternative for these purposes.

Notwithstanding the Applicants' characterization of any information as being confidential, the foundation is under no obligation to treat such information as confidential.

Disclaimer

This document is not an award or promise of a grant or contract. All awards are subject to the approval and processes of the foundation as well as all required documentation. All awards are subject to the terms and conditions of the foundation reflected in separate written agreements signed by the foundation. The foundation assumes no responsibility for the Applicants' cost to respond to this Grand Challenge. All documents submitted in connection with this Grand Challenge become the property of the foundation.

Release and Verification

In exchange for the opportunity to be awarded a grant or contract, the Applicant agrees that the foundation may, in its sole discretion: (1) amend or cancel the Grand Challenge, in whole or in part, at any time; (2) extend the deadline for submitting responses; (3) determine whether a response does or does not substantially comply with the requirements of the Grand Challenge; (4) waive any minor irregularity, informality or nonconformance with the provisions or procedures of the Grand Challenge; (5) issue multiple awards; (6) share responses generated by this Grand Challenge with foundation staff, consultants, contingent workers, subject matter experts, and potential co-funders; and (7) copy the responses.

Applicant agrees not to bring a legal challenge of any kind against the foundation relating to the foundation's selection and award of a grant or contract arising from this Grand Challenge.

Applicant represents that it has responded to the Grand Challenge with complete honesty and accuracy. If facts provided in Applicant's response change, Applicant will supplement its response in writing with any deletions, additions or changes within ten days of the changes. Applicant will do this, as necessary, throughout the selection process. Applicant understands that any material misrepresentation, including omissions, may disqualify it from consideration for a grant or contract award.

By responding to this Grand Challenge, you are representing: (i) that you have authority to bind the named Applicant to the terms and conditions set forth above, without amendment; and (ii) that you agree to be bound by them.

Global Access and Intellectual Property

Intellectual property (IP) rights and the management of IP rights are likely to play an important role in achieving the goals of this project. To this end, the foundation requires that, even at this stage, all applicants seriously consider their willingness to submit a response in compliance with the foundation's response requirements, a portion of which may ask for certain information and intentions regarding intellectual property concerns and Global Access. Specifically, the foundation requires that:

You will conduct and manage the Project and the Funded Developments in a manner that ensures Global Access. Your Global Access commitments will survive the term of the Agreement. "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 You or a third party prior to or outside of the Project used as part of the Project. "Global Access" means: (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.

More information about the foundation's global access approach can be found at:
http://www.gatesfoundation.org/Global-Access

Research Assurances

While not necessary for the LOI application, as applicable to the individual project, the foundation will require that for each venue in which any part of the project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. The foundation will further require the Applicant to agree that no funds will be expended on studies enrolling human subjects or involving animals until all necessary regulatory and ethical bodies' approvals are obtained.