BILL & MELINDA GATES foundation

NIMBL

The National Institute for Innovation in Manufacturing Biopharmaceuticals

THE GLOBAL HEALTH FUND

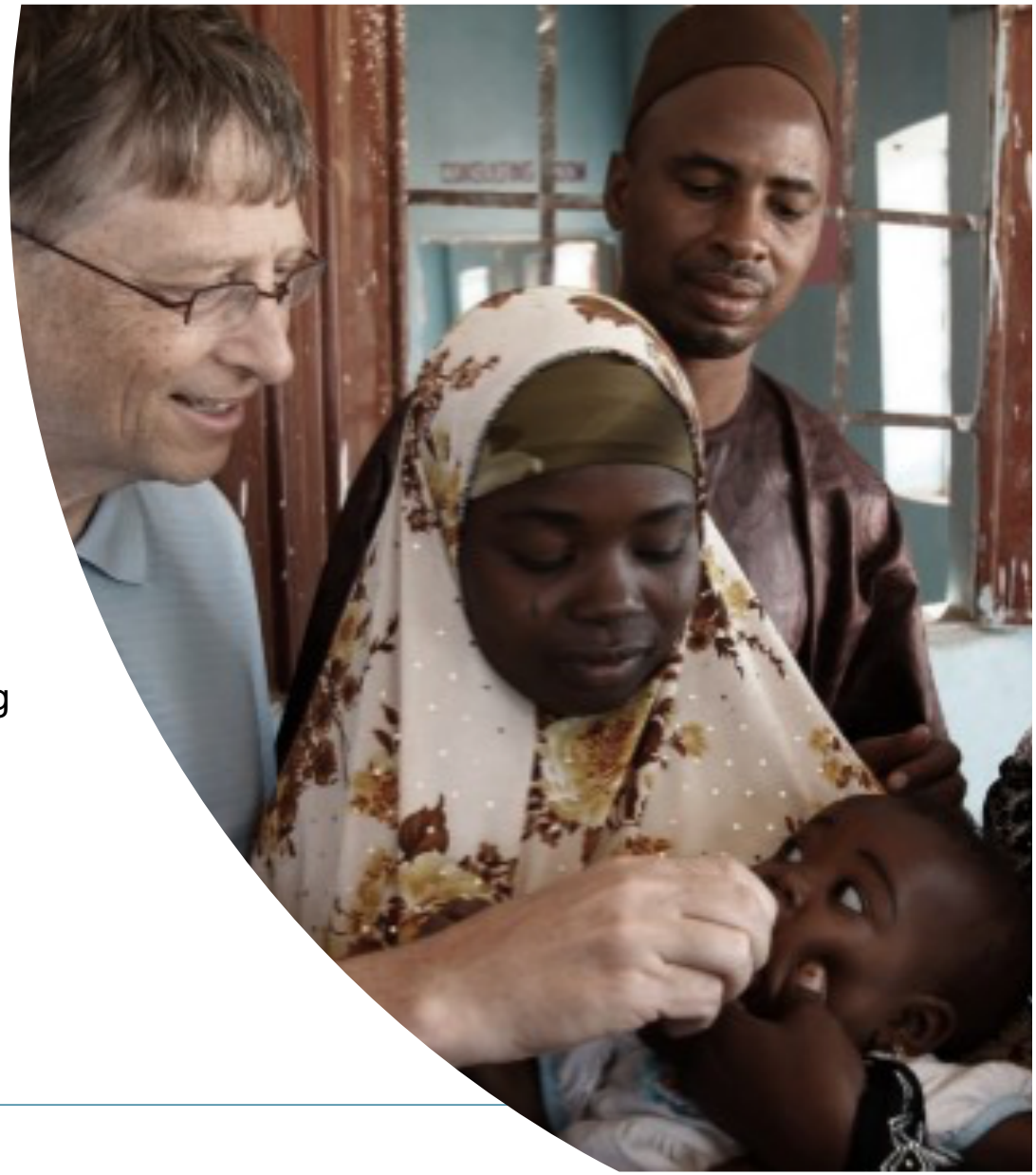
RAY PRASAD

GATES GLOBAL HEALTH FUND

The Bill & Melinda Gates Foundation in partnership with the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) has established a pilot ‘Global Health Fund’.

It supports the development and implementation of innovative technologies for vaccine and biological manufacturing to accelerate development timelines, lower cost of manufacturing, secure supply for GAVI and ensure appropriate product profiles for their geographies including new combinations and novel vaccine.

NIIMBL is seeking technologies relevant to remediate manufacturing gaps of the Developing Country Vaccine Manufacturing Network (DCVMN) community.



BENEFITS OF PUBLIC-PRIVATE PARTNERSHIP

- Knowledge / experience sharing
- De-risking technology adoption
- Leveraging investments for technology advancement

WHAT NIIMBL FOCUSES ON

NIIMBL executes technology innovation projects across a variety of biomanufacturing needs with the goal of enhancing patient access to medicines.

This includes initiatives on vaccines, antibodies, proteins, and advanced therapies.

To date, ~60 projects have been authorized or launched representing more than $60 million USD of investment.

Teams include large and small companies, government scientists, local governments, universities, and other nonprofits.

NIIMBL IS…

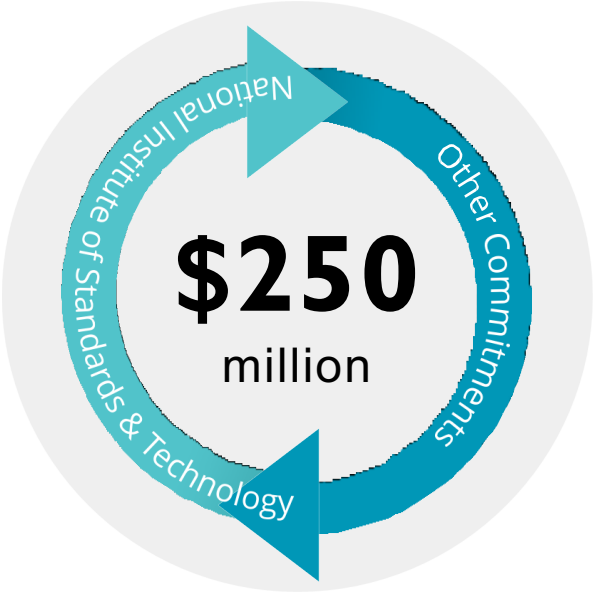
- A place where industry, academic, state, and U.S. federal resources synergize to:
  - meet industry's needs,
  - de-risk and streamline process development & manufacturing, and
  - train a growing workforce.
- Enhanced process robustness is obtained
- Major manufacturers work with suppliers to develop new technologies
- Standardization of interfaces, assays, parts, and certifications is achieved
- New methods, technologies, and best practices are demonstrated collaboratively with health authorities
- Workforce creation matches industry needs

NIIMBL FUNDING – ESTABLISHED 2017

NIIMBL
The National Institute for Innovation in Manufacturing Biopharmaceuticals

$70,000,000
National Institute of Standards and Technology

NIST



$180,000,000
Other Commitments

NIIMBL is funded by a $70,000,000 cooperative agreement from the National Institute of Standards and Technology and leverages >$180,000,000 in other commitments.

NIST is a non-regulatory federal agency within the U.S. Department of Commerce. NIST's mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life.

NIIMBL VACCINES TECHNOLOGY ROADMAP

Roadmap published in 2018 in collaboration with industry, academia and government

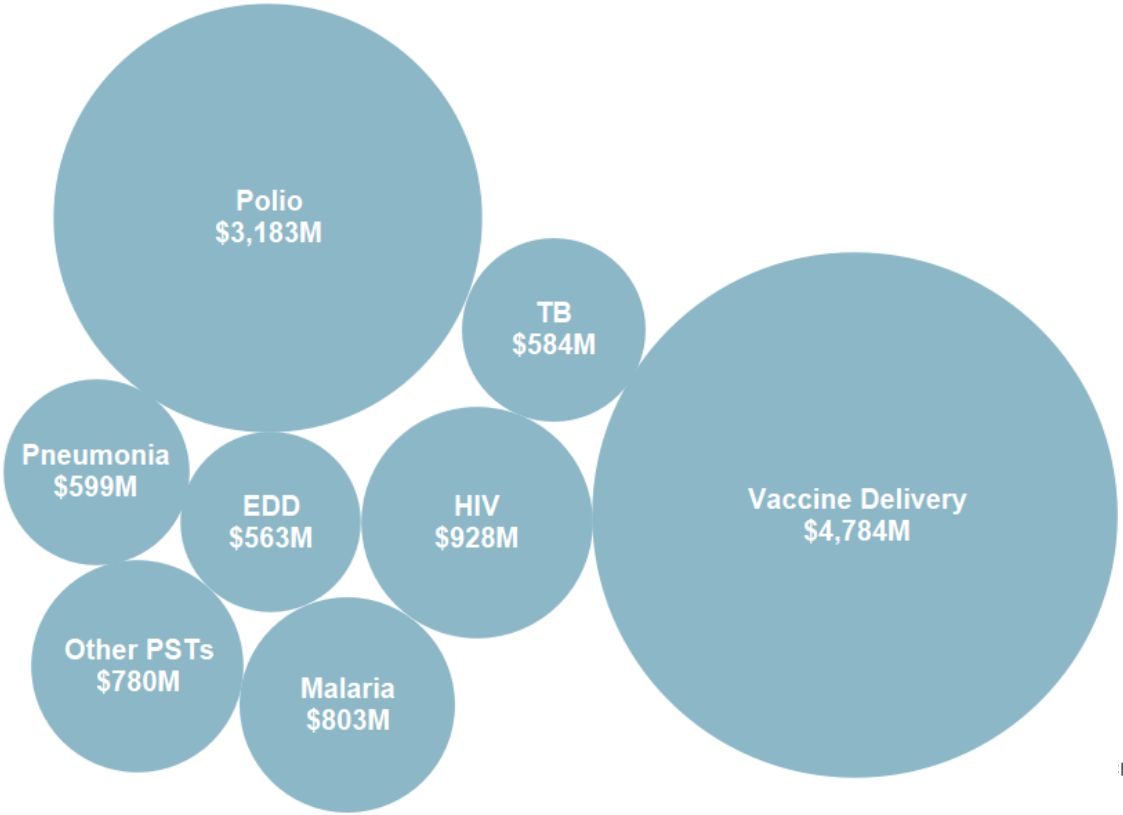
Recommendations

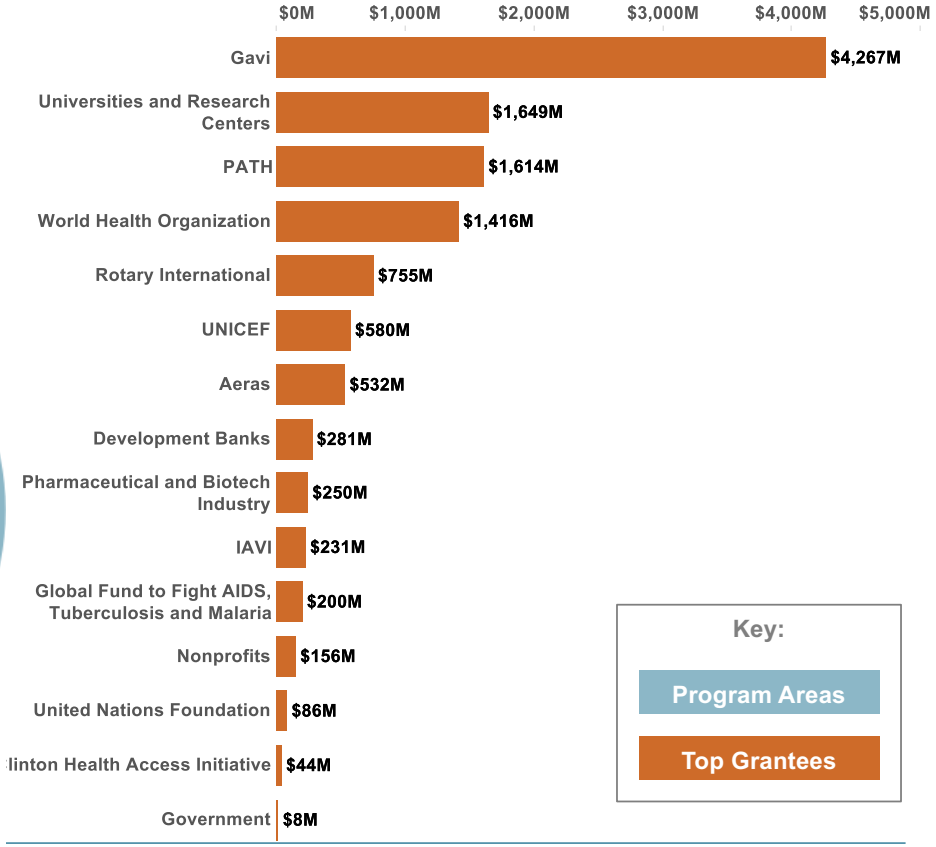
- continued **investment** in innovation (e.g. pipelines to address new infectious diseases; robust, reliable supply with a low cost of goods (CoGs); enabling safe, effective and quality products)
- simple and clear **regulatory** pathways, especially for enabling innovative approaches for vaccine process, analytics and formulation solutions
- **collaboration** among manufacturers, suppliers, regulators and research communities

WHAT BMGF FOCUSES ON

THE GATES FOUNDATION INVESTS HEAVILY IN VACCINES

BMGF has committed significant investments for vaccine policy, country systems, markets and product development to make life-saving vaccines available to developing countries and improve uptake





Source: BMGF vaccine investment analysis (amount paid and committed), 1998-2020

WORK WILL BE ANCHORED TO OUR "NORTH STAR" VISION

All countries and individuals can access vaccines whenever needed

All countries and individuals have a reliable supply over the next 10-20 years

Within WHO definition of a "fully immunized child"

To ensure a **secure** and **sustainable** supply of **consistently high quality, appropriately priced vaccines** that meet the **needs of users**

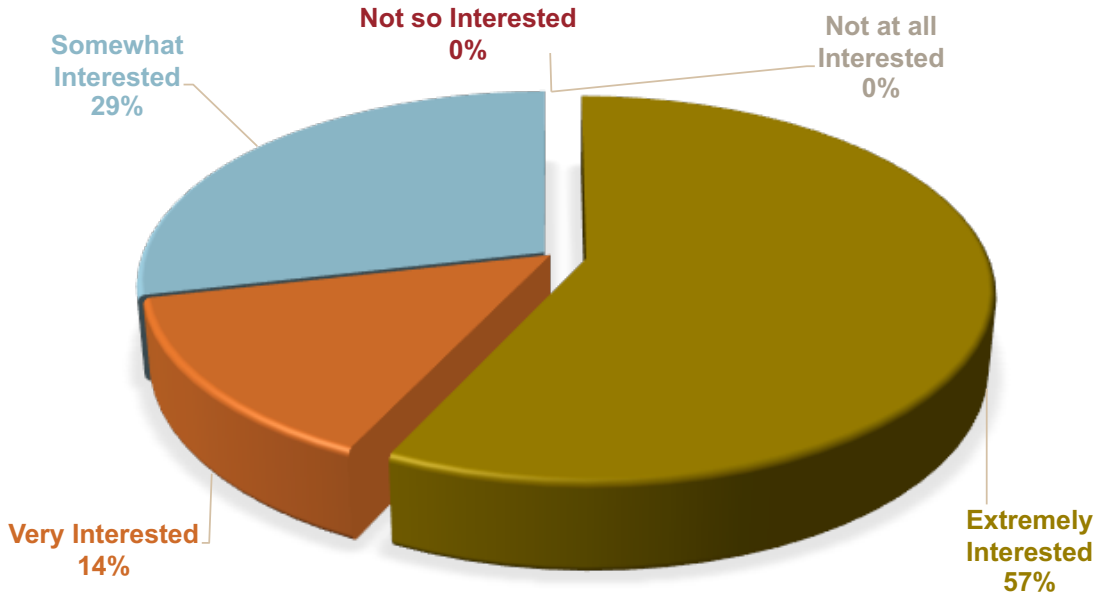
Meet WHO prequalification standards (or equivalent)

Have the characteristics and packaging which enable maximum coverage and use

Varied by market to account for ability to pay and need for financial incentive to spur development

BMGF-NIIMBL SURVEY RESULTS

Are the areas of reduction of Animal Testing – Development of alternative *in vitro* assays to reduce the amount of animal testing required for lot release of interest to your company?



Number of Respondents: 14

NOTIONAL PROJECT CALL IDEAS FOR THE GLOBAL HEALTH FUND

#	Topic	Description
1	Reduction of Animal Testing	Development of alternative *in vitro* assays to reduce the amount of animal testing required for lot release
2	Recombinant Albumin	Development of low-cost sources of recombinant albumin to reduce vaccine costs and ensure greater supply security
3	Universal Buffer Skids	Develop universal buffer distribution system to be used for key chromatography, ultrafiltration and microfiltration steps.
4	Process Analytics & Control	Develop more reliable sensors for pH, CO2, and O2 as well as for key metabolites, feed strategies, viability, cell density, bioburden, endotoxin, rapid contamination identification, and rapid sterility tests
5	Rapid release of drug substance and drug product	Develop improved assays for adventitious agents with goal of reducing testing time
6	Single use equipment	Evaluate improved materials for use with single use equipment. Develop standardized fittings across vendors
7	High concentration MAb formulation	Novel technologies to increase MAb concentration in liquid formulations to allow SC administration of high doses
8	Automation	Creation of integrated technologies that perform on-line analytics and in process controls that relieve the requirement for significant training and support PAT by combining analytical and statistical tools to improve manufacturing operations and ensure regulatory compliance. Reduces contamination risks and increases overall quality of products.
9	Supply chain	Innovative ideas to ensuring adequate supply of qualified raw materials, consumables, starting materials, service providers, and manufacturing equipment
10	Training innovations	VR and/or immersive reality training for operations of DCVM facilities as well as design optimization.

KEY ISSUES WITH ANIMAL TESTING

- Variability across labs, animals, operators, environment, animal food, etc.[1, 2]
- Precision of testing
- Sourcing and maintaining the animals
- Difficulty getting a sufficient quantity of animals
- Different requirements from different regulatory bodies[3]
- Animal studies are expensive and time consuming[4]
  - Results of potency tests available after 2 months
  - Shelf-life of several vaccines limited to about 2 years

[1]Hendriksen CF1, Slob W, vd Gun JW, Westendorp JH, den Bieman M, Hesp A, van Zutphen LF. Immunogenicity testing of diphtheria and tetanus vaccines by using isogenic mice with possible implications for potency testing. *Lab Anim*. 1994 Apr;28(2):121-9.
[2]Manual for Quality Control of Diphtheria, Tetanus and Pertussis Vaccines. World Health Organization Department of Immunization, Vaccines and Biologicals.
[3]Recommendations for diphtheria, tetanus, pertussis and combined vaccines, Annex 5 (Amendments 2003). World Health Organization, WHO Technical Report Series, No. 927, 2005
[4]Adapted from: *Three Rs achievements in vaccinology*. *AATEX* 14, Special Issue, 575-579 Proc. 6th World Congress on Alternatives & Animal Use in the Life Sciences August 21-25, 2007, Tokyo, Japan

ANIMALS USED IN DS AND DP QC RELEASE TESTS

DS release		
Purpose	**Type of Animal**	**# of Animals/batch**
TT	Guinea pig	17
DT	Guinea pig	16
Inactivated wP	Mouse	30
Hib	Guinea pig	8
DP release		
Purpose	**Type of Animal**	**# of Animals/batch**
HepB	Mouse	180
D	Guinea pig	16
T	Mouse	25
D/T	Guinea pig	5
wP	Mouse	230
IPV	Wistar rat	80
General	Mouse	10
	Guinea pig	4

[1]Data courtesy of LG Chemicals, email dated 25MAR2019

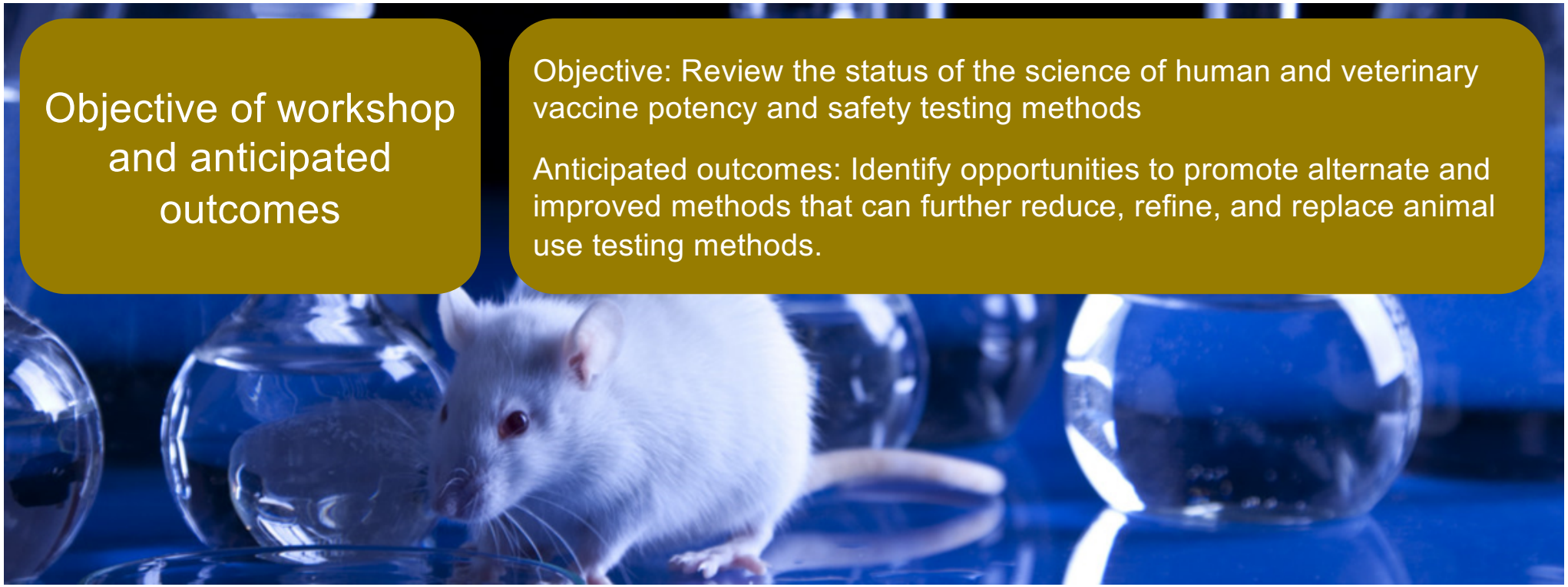
NIIMBL-BMGF GLOBAL HEALTH FUND (GHF) INITIAL PROJECT CALL

The topic area for this call is replacing animal-based release testing for vaccines, which was identified from survey responses with DCVMN members followed by a community workshop to explore alternative approaches to animal-based release testing.

Project Call 3.1 Topics

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

REPLACEMENT OF ANIMAL TESTING BY IMPROVED VACCINE POTENCY TESTS FOR LEGACY VACCINES SUCH AS TETANUS, DIPHTHERIA, PERTUSSIS AND POLIO



Objective of workshop and anticipated outcomes

Objective: Review the status of the science of human and veterinary vaccine potency and safety testing methods

Anticipated outcomes: Identify opportunities to promote alternate and improved methods that can further reduce, refine, and replace animal use testing methods.

VACCINES SELECTED BASED ON PRIORITY

1. Polio
2. Whole Cell Pertussis
3. Rabies

GLOBAL HEALTH FUND (GHF) INITIAL PROJECT CALL

The GHF process involves a two-stage process:

1. Submission of short Concept Papers
2. Invitations for Full Proposals

Project participants are expected to cost share on project costs.

Some terms and conditions apply to funded teams (open access rights, etc.).

GLOBAL HEALTH FUND (GHF) INITIAL PROJECT CALL

Concept Papers were submitted by September 10, 2019.

A GHF Summit will be held on October 25, 2019 in the Washington DC area for concept proposers to present and discuss their ideas with key stakeholders for the purpose of evaluation. The Summit also provides proposers an opportunity for networking and teaming discussions. Fifteen concepts from twelve different organizations have been invited to present at the GHF Summit.

Based on evaluation feedback, selected concepts will be invited to the second stage - submission of a Full Proposal. The full proposals submitted will undergo subject matter expert review and evaluation.

The current GHF project call funding determinations are expected to be made in April 2020.

GLOBAL HEALTH FUND (GHF) STEERING COMMITTEE

A GHF Steering Committee is being formed to provide strategic guidance for the GHF.

The Steering Committee will be charged with:

- making recommendations for funding of GHF proposals to the NIIMBL Governing Committee to inform project funding determinations
- guiding the direction of future GHF priorities, including contributing to the development of future workshops with a focus likely on vaccines and low-cost manufacture of therapeutic proteins such as antibodies. There are plans to hold a Vaccine Technology workshop in early 2020. The Steering Committee will look to benefit from important guidance from the DCVMN.

The Steering Committee will be comprised of representatives from NIIMBL industry member organizations, NIIMBL leadership, and the BMGF.

WE ENCOURAGE YOUR ENGAGEMENT WITH THE GHF

The Global Health Fund is expected to be ongoing with funding made available for future Project Calls and planning for this is underway.

GROUPS WORKING TO REDUCE ANIMAL TESTING

DCVMN

dcvmn
Developing Countries Vaccine Manufacturers Network

WHO

World Health Organization

FDA

FDA

3Rs

IABS

IABS

NIMBL

NIMBL
The National Institute for Innovation in Manufacturing Biopharmaceuticals

Collaboration between all groups and regulators will be a key to success

THANK YOU

BMGF-NIIMBL SURVEY RESULTS (CONT.)

WHAT CAVEATS WOULD YOU ADD TO ANY OF THE AREAS SUGGESTED (IN A PREVIOUS QUESTION)?

RESPONDENT	CAVEATS TO REDUCTION OF ANIMAL TESTING
R1	No response
R2	Considering the animal welfare, in-vitro potency test replace in-vivo potency test as the release test items is the priority choice.
R3	No response
R4	genetic and sanitation control
R5	Reducing number of experimental animals
R6	Challenging in case of vaccines where no protective correlates of vaccine are established. Challenging for established vaccines.
R7	No response
R8	needs for reliable in vitro assay
R9	Not only achieving the correlation data between pre- and post-test methods but also recognition from NRAs of advanced countries should be premised
R10	No response
R11	No response
R12	No response
R13	Cost effective & faster without compromise on Product Quality