REPORT NO.: RES28423

RESTRUCTURING PAPER

ON A

PROPOSED PROJECT RESTRUCTURING

OF

SUPPORT TO RESEARCH AND DEVELOPMENT AT THE INTERNATIONAL AIDS VACCINE INITIATIVE

APPROVED ON FEBRUARY 10, 2017

TO

INTERNATIONAL AIDS VACCINE INITIATIVE

HEALTH, NUTRITION & POPULATION

OTHER

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ABBREVIATIONS AND ACRONYMS

AIDS	—	Acquired Immune Deficiency Syndrome
DNA	—	Deoxyribonucleic Acid
FMR	—	Financial Management Report
GMP	—	Good Manufacturing Practice
HIV	—	Human Immunodeficiency Virus
IAVI	—	International AIDS Vaccine Initiative
VSV	—	Vesicular Stomatitis Virus
US	—	United States

Note to Task Teams: The following sections are system generated and can only be edited online in the Portal.

BASIC DATA

Product Information

Project ID P161232	Financing Instrument Investment Project Financing
Original EA Category Partial Assessment (B)	Current EA Category Partial Assessment (B)
Approval Date 10-Feb-2017	Current Closing Date 30-Jun-2017

Organizations

Borrower International AIDS Vaccine Initiative	Responsible Agency International AIDS Vaccine Initiative

Project Development Objective (PDO)

Original PDO

The Project Development Objective is to support the International AIDS Vaccine Initiative (IAVI) in the optimization and testing of one HIV vaccine candidate.

Summary Status of Financing

TF	Approval	Signing	Effectiveness	Closing	Net Commitment	Disbursed	Undisbursed
TF-A4434	08-Feb-2017	27-Feb-2017	27-Feb-2017	30-Sep-2018	1.80	1.80	0

Policy Waiver(s)

Does this restructuring trigger the need for any policy waiver(s)?

No

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I. PROJECT STATUS AND RATIONALE FOR RESTRUCTURING

1. The Implementation Status Report dated May 30, 2017 assessed the status of implementation of project activities and progress towards the Project Development Objectives and rated the Project as moderately satisfactory. The Project experienced delays related to staff turnover and problems with the supplier of DNA templates necessary for research. To date, all issues have been resolved, and both Components 1 and 2 have been implemented.

2. Key achievements include: five new recombinants were generated and viable vaccine vectors were characterized *in vitro* to identify lead candidates that demonstrate high replication rate and stability. The International AIDS Vaccine Initiative (IAVI) produced a vaccine candidate and launched a comparative vaccine study in Indian rhesus macaques to analyze its safety, immunogenicity and efficacy.

3. The Government of Japan views the search of a cure against HIV/AIDS as an important part of its Global Health Security agenda and has expressed interest in continuing the support of research and development of an HIV vaccine at IAVI. The Ministry of Finance (Japan) will contribute an additional US$ 2 million to the World Bank Trust Fund to continue the current program of research at IAVI. Therefore, the proposed project restructuring and additional financing is expected to expand the research program by adding new components, adjusting the Results Framework, and extending the closing date of this Small Grant.

4. The overall rating against the achievement of the PDO is “Highly Satisfactory”, as both components 1 and 2 have been implemented. Financial Management is rated “Highly Satisfactory”, and there are no pending issues. FMR reports will be submitted on time.

II. DESCRIPTION OF PROPOSED CHANGES

1. The purpose of the restructuring is to process additional financing in the amount of US$ 1,792,146 from the Government of Japan and to continue a research program (total grant amount is US$ 3,593,757) The PDO of the project will remain the same (“to support IAVI in the optimization and testing of one HIV vaccine candidate”). The closing date of the grant has been extended to September 30, 2018.

2. The restructuring proposes the following changes:

    a. **Change in Results Framework**: New indicators are added to monitor the implementation of the next phase of the project.
    b. **Change in Components and Cost**: New Components are added to expand the research program based on achievements made to date. These will include the following:
        i. **Component 1: Comprehensively evaluate the new VSVdG-Env.BG505.1 vaccine vector *in vitro* and produce a vaccine seed** that can be rapidly advanced for GMP manufacturing if preclinical immunogenicity and efficacy data supports transition to a clinical development program. This

Component will entail: 1) additional *in vitro* characterization of the vaccine and the Env immunogen it delivers, and 2) immunologic and virologic evaluation of samples developed by IAVI from this vaccine vector candidate. The cumulative data generated by these activities is essential to assess VSVdG-Env.1 and determine if it merits continued development. Planning for a positive outcome from these studies, IAVI also will derive a vaccine seed using Good Laboratory Practices that can be rapidly transferred to a contract manufacturer if preclinical data supports entry into a clinical development program.

ii. **Component 2: Develop vectors with alternative strategic modifications designed to enhance the Env antibody response induced by VSVdG-Env vaccines**. IAVI will continue parallel investigation of two alternative vector designs. The first alternative is to continue investigating the effect of Env gene position in the VSV genome. Vectors with Env in position 2, 3 and 5 will be developed for comparison to VSVdG-Env.BG505.1 (position 1) and the prototype (gene position 4). The end goal is to identify a vector with greater replicative capacity than the prototype VSVdG-Env.BG505 vaccine and VSVdG-Env.BG505.1, and expresses increased quantities of Env compared to the prototype. In the second strategy, the goal is to modulate the immune response induced by VSV. The new vector will be evaluated *in vitro* to verify genetic stability of the M-gene mutations and confirm that replicative capacity is maintained and will support production of vaccine material. It is anticipated that 1-3 new candidate vectors will emerge from the Component 2 that merit further testing. Vector candidates are sub-vectors and part of the testing of an overall ideal candidate vaccine.
    - **Component 2.1: Develop at least one additional vector that can be used for development of VSVdG chimeric virus vaccines**. The current VSVdG vector is based on VSV Indiana, however, repeated use of the same vector to deliver multiple different vaccines will induce inhibitory anti-vector immunity. Thus, it will be important to develop additional vectors based on VSV relatives that do not evoke strong cross-reactive immune responses against the VSV structural proteins.

iii. **Component 3: Develop a new Vero cell line that will support replication of VSVdG-Env and produce virus particles bearing a VSV G glycoprotein pseudotype**. This cell line technology is needed to support more robust large-scale manufacturing of a VSVdG-Env.BG505 vaccine product. Development of the cell line will include design and testing of gene constructs expressing the three glycoproteins, extensive characterization of the new cell lines, and demonstration that they support reproducible production of high yields of pseudotyped virus particles.

iv. **Component 4. Dissemination of knowledge during the 2017 Universal Health Coverage Forum in Tokyo**. The side event will be organized to disseminate the findings of current research program and stimulate interest in further investment into research and development of an HIV vaccine as a global public good.

v. The proposed research plan entails development of multiple vaccine vectors that are part of the testing of an overall ideal candidate vaccine.

c. **Change in Overall Risk**: the new components of the project do not entail research in animal subjects, and the proposed program of research is more discrete and has more predictable outputs than the previous year's program. Hence a downgrade in overall risk has been made from "Moderate" to "Low".
d. **Procurement and Financial Management Plan will be revised accordingly to reflect new components and the revised Implementation Schedule**.

3. The eligible expenditures by components are set forth:

Project components	Project cost, USD	Percentage of expenditures to be financed, %
Component 1	916,989	100%
Component 2	408,726	100%
Component 3	444,125	100%
Component 4	22,306	100%
Total financing required	**1,792,146**	**100%**

a. By categories of expenditure:

Category	Amount of the grant allocated (USD)	Percentage of Expenditures to be financed (inclusive of taxes)
Goods (purchase of a plate washer and a stacking unit)	39,660	100%
Incremental Operating Costs	1,732,486	100%
Workshops, trainings, and conferences	20,000	100%
Total financing required	1,792,146	100%

4. For purposes of this Grant, the term “Incremental Operating Costs” means the reasonable cost of incremental expenditures incurred by the Recipient on account of Project implementation consisting of laboratory operating expenses, which include office rental, utilities, laboratory equipment maintenance, salaries of staff of the Recipient assigned to Project implementation, support and oversight; and laboratory supplies and laboratory and office consumables; and (ii) “Training and Workshops” means the reasonable costs, as shall have been approved by the World Bank, for training and workshops conducted under the Project, including travel and subsistence costs for training and workshop participants, costs associated with securing the services of trainers and workshop speakers, rental of training and workshop facilities, preparation and reproduction of training and workshop materials, and other costs directly related to training course and workshop preparation and implementation (but excluding goods and consultants’ services).

5. Details of all the changes are reflected in the following sections.

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I. SUMMARY OF CHANGES

	Changed	Not Changed
Change in Results Framework	✓	
Change in Components and Cost	✓	
Change in Loan Closing Date(s)	✓	
Additional Financing Proposed	✓	
Change in Overall Risk Rating	✓	
Change in Procurement	✓	
Change in Implementation Schedule	✓	
Change in Implementing Agency		✓
Change in Project's Development Objectives		✓
Cancellations Proposed		✓
Reallocation between Disbursement Categories		✓
Change in Disbursements Arrangements		✓
Change in Disbursement Estimates		✓
Change in Safeguard Policies Triggered		✓
Change of EA category		✓
Change in Legal Covenants		✓
Change in Institutional Arrangements		✓
Change in Financial Management		✓
Other Change(s)		✓

IV. DETAILED CHANGE(S)

RESULTS FRAMEWORK

Project Development Objective Indicators

Vector has been optimized
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	Yes	Yes	No Change
Date	04-Jul-2016	30-Jun-2017	30-Jun-2017	

Vector testing has been initiated
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	Yes	Yes	No Change
Date	04-Jul-2016	30-Jun-2017	30-Jun-2017	

VSVdG-Env.BG505.1 vaccine vector has been evaluated
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	06-Sep-2017		29-Jun-2018	

Additional viral vectors have been developed
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	06-Sep-2017		28-Sep-2018	

Intermediate Indicators

Five genetically modified VSVdG-Env.BG505 vaccines have been isolated and characteristics have been analyzed
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	Yes	Yes	No Change
Date	10-Feb-2017	30-Jun-2017	01-Mar-2017	

VSVdG-Env.BG505 mutants have been isolated after serial passage under conditions that select for viruses with increased replicative fitness. Mutant virus characteristics have been analyzed.

Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	Yes	Yes	No Change
Date	10-Feb-2017	30-Jun-2017	01-Mar-2017	

A decision to test new VSVdG-Env.BG505 vaccines or revise a macaque study to evaluate the requirement for three doses have been made.
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	Yes	Yes	No Change
Date	10-Feb-2017	30-Jun-2017	31-Mar-2017	

Candidate vaccines have been produced for a preclinical study.
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	Yes	Yes	No Change
Date	10-Feb-2017	30-Jun-2017	01-Jun-2017	

Preclinical study in non-human primates has been commenced.
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	Yes	Yes	No Change
Date	10-Feb-2017	30-Jun-2017	30-Jun-2017	

Determination of construction feasibility and replicative capacity of VSVdG-Env.BG505 with Env in position 2, 3 or 5
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	20-Jun-2017		02-Apr-2018	

VSVdG-Env.BG505 position 1 vector with Matrix protein (M) modifications that will dampen the innate immune response rescued

Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	20-Jun-2017		01-Jan-2018	

VSVdG-Env.BG505.1 vector with M modifications evaluated for genetic stability and replicative capacity
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	20-Jun-2017		28-Sep-2018	

Initiate VSVdG-Env.BG505 position 1 vector vaccine rescue in Early Development Laboratory
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	20-Jun-2017		28-Sep-2018	

Feasibility of VERO-CD4/CCR5 cell line also expressing VSV glycoprotein G is demonstrated
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	20-Jun-2017		29-Dec-2017	

Conduct serial passage of VSV New Jersey vector to improve replicative capacity and fitness of the virus
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	20-Jun-2017		29-Dec-2017	

Evaluate VSV New Jersey vector for improved fitness and utility as a vaccine platform
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	20-Jun-2017		28-Sep-2018	

Initiate VERO CD4/CCR5 VSV G expressing cell line in Early Development Laboratory
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	06-Sep-2017		28-Sep-2018	

Organize and facilitate meeting in conjunction with UHC Forum in December in Tokyo on Japanese investments in global health R&D
Unit of Measure: Yes/No
Indicator Type: Custom

	Baseline	Actual (Current)	End Target	Action
Value	No	No	Yes	New
Date	06-Sep-2017		01-Jan-2018	

COMPONENTS

Current Component Name	Current Cost (US$M)	Action	Proposed Component Name	Proposed Cost (US$M)
Vector Optimization. Five new recombinant vaccines will be generated, their specificity will be tested along with vaccine strain prototype VSVdG-Env.BG505	0.71	No Change	Vector Optimization. Five new recombinant vaccines will be generated, their specificity will be tested along with vaccine strain prototype VSVdG-Env.BG505	0.71
Vector Testing. Production of two vaccine candidates and a launch of a comparative vaccine study in Indian rhesus macaques to analyze safety, immunogenicity, and efficacy.	1.09	No Change	Vector Testing. Production of two vaccine candidates and a launch of a comparative vaccine study in Indian rhesus macaques to analyze safety, immunogenicity, and efficacy.	1.09
	0.00	New	Presentation of research in	0.02

				conferences and workshops	
		0.00	New	Develop a new Vero cell line that will support replication of VSV□G-Env and produce virus particles bearing a VSV G glycoprotein pseudotype.	0.44
		0.00	New	Develop vectors with alternative strategic modifications designed to enhance the Env antibody response induced by VSVG-Env vaccines; Develop at least one additional vector for VSVdG virus vaccine.	0.41
		0.00	New	Comprehensive evaluation of VSVdG-Env.BG505.1 vaccine vector. Production of a vaccine seed.	0.92
TOTAL		**1.80**			**3.59**

LOAN CLOSING DATE(S)

TF	Status	Original Closing	Revised Closing(s)	Proposed Closing	Proposed Deadline for Withdrawal Applications
TF-A4434	Effective	30-Jun-2017	30-Sep-2018	30-Sep-2018	30-Jan-2019

ADDITIONAL FINANCING

Source	Currency	Amount	USD Equivalent
Free-standing TFs for HDNVP(FSHD)	USD	1,792,146.00	1,792,146.00
		Existing Net Commitment USD Amount	1,800,000.00
		Total	**3,592,146.00**

OVERALL RISK RATING

Risk Category	Rating at Approval	Current Rating
Overall		Low

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