

CONSORTIUM AGREEMENT FOR MULTI-PARTNER COLLABORATIVE PROJECT ON PSPT ASSAY VALIDATION

THIS AGREEMENT is made the 29th day of JULY 2020 BETWEEN

The State of the Netherlands, represented by the Minister of Public Health, Welfare and Sports, on behalf of the Minister, Projectdirectie ALT, The Institute for Translational Vaccinology (Intravacc), AND

INSTITUTE OF BIOLOGICAL PRODUCTS with laboratories at 88/7 Soi Bamrathnaradura, Tivanond Rd., Amphur Muang, Nonthaburi 11000, Thailand, AND

NATIONAL QUALITY CONTROL LABORATORY OF INDONESIAN FOOD AND DRUG AUTHORITY with laboratories at Jl. Percetakan Negara No. 23 Jakarta Pusat 10560, Indonesia, AND

THE SERUM INSTITUTE OF INDIA Pvt. with laboratories at 212/2, Hadapsar, Pune - 411028 (Maharashtra) India, AND

BHARAT BIOTECH INTERNATIONAL LIMITED OF INDIA with laboratories at Genome Valley, Turkapally, Shameerpet, Hyderabad-500078, India, AND

BIOLOGICAL E LIMITED OF INDIA with laboratories at Plot No 1 Biotech park Phase II, Genome Valley Shameerpet Hyd -500078 India, AND

PASTEUR INSTITUTE OF INDIA, COONOR, The Nilgiris, Tamilnadu, AND

BIO FARMA OF INDONESIA with laboratories at Pasteur 28 Bandung West Java Indonesia, AND

PANACEA BIOTEC LIMITED OF INDIA with laboratories at Malpur, Baddi-173205, Himachal Pradesh, India, AND

SANOFI HEALTHCARE INDIA PRIVATE LIMITED with laboratories at H.No.5-10-173, 3rd & 4th Floors, Vasantha Chambers, Fateh Maidan Road Basheerbagh, Hyderabad, Telangana, 500004, AND

BULBIO-NCIPD LTD with laboratories at 26 Yanko Sakazov Blvd., 1504 Sofia, Bulgaria, AND

DCVMN International, Route de Crassier, 7, CH-1262, Nyon, Switzerland.

(hereinafter referred to individually as a 'Party', collectively or in groups as 'Parties')

Introduction:

A. The Parties to this Agreement wish to undertake a project entitled 'International multi-laboratory in-house validation of the Pertussis Serological Potency Test (PSPT) in mice compared to the in vivo challenge Mouse Protection Test (or Kendrick Test) for whole-cell Pertussis (wP) vaccine batch testing'.

B. The Parties intend to carry out a programme of work which is described in Annex 1 [attached] (hereinafter referred to as the 'Project').

C. The 1.5 years Project will involve the in-house validation and implementation of an ELISA test for the assessment of the potency of whole-cell Pertussis containing vaccines, relative to an in-house vaccine of the same composition and to a regional reference preparation and the statistical analysis of data sets collected from the various laboratories (hereinafter referred to as 'Deliverables', see Annex 1).

This Agreement sets out the details of the relationship between the Parties.

It is hereby agreed as follows:

1. Purpose of the Consortium

The Consortium represents an informal collaboration (without assets) of laboratories formed to undertake the Project.

The Project is performed by the members which are the signatories of this Consortium Agreement and executing laboratory related work at own costs, except for the provision of coating antigen aliquots and independent statistical analysis, and reporting (including perhaps a publication) that will be covered by DCVMN.

The purpose of the Consortium is to carry out the Project individually, in the respective laboratories of the consortium members, using their own expertise, staff, supplies, reagents, animals and equipment, to produce the "Deliverables" as described. The Deliverables is the result of the execution of activities agreed by the Consortium members for the in-house validation of the PSPT assay and described in Annex 1.

Titration of antibodies purified from the peripheral blood of immunized mice will be determined in ELISA plastic plates coated with the cells of Bordetella pertussis (whole cell-wC-strain 18323, the same strain used in the challenge for Mice Protection Test – (MPT).

The Bordetella pertussis whole cell-wC-strain 18323 coating antigen for the ELISA plates used in the titration will be provided free of charge by DCVMN to all consortium laboratories.

Protocols (SOPs) for the performance of the Pertussis Serological Potency Test (including mice immunization, bleeding, and ELISA) will be used in order to make consistent performance of PSPT testing.

The in-house validation is to be executed using commercial antigen/vaccine batches available at each laboratory and each laboratory has to produce its own altered batch from one of the commercial batches used, so that the Mouse Protection Test will be performed by the quality control laboratory staff as part of their routine quality testing procedures for wP containing vaccines, and by National Control Laboratories within their routine batch release testing activities.

Each participating laboratory is responsible to communicate with its own regulatory authority or National Control Laboratory, at their earliest and best convenience, to inform about their plan and activities to validate the in-house the PSPT.

2. Commencement and duration

The Consortium will be formed and the Project will become effective from the last date of the signature by the fifth participating laboratory and the Project has a duration of 1.5 years, unless otherwise agreed to be extended or terminated in writing by all the Parties.

This agreement is at-will and may be modified by mutual written consent. This agreement shall become effective upon the last date of signature by the fifth participating laboratory and will remain for the duration of the Project in effect until modified or terminated by any one of the Parties. In the absence of mutual agreement by the authorized signatories for modification or extension this Consortium Agreement shall automatically end on 31st December 2021, or it will be amended if necessary.

3. Project resources

The Consortium budget is composed of two main parts: the NIIMBL supported activities and the Cost-share provided by grantee as in-kind contributions, and should be at least 1:1 proportion (i.e. NIIMBL award should not be higher than the in-kind cost-share). The NIIMBL provided funds are awarded to the organization serving as Project Lead, and member of NIIMBL, that will serve as administrator of the NIIMBL awarded funds. The in-kind contributions are to be documented, for the record, while there will be no transfer of funds between the participating laboratories and the Consortium administrator (DCVMN Secretariat).

The award to the Project shall be administered by DCVMN International, aimed at covering specific services and events required to carry out the Project, in accordance with the schedule detailed in Annex 2.

The Consortium is to be responsible for all the costs, in the respective laboratories, for their own expertise, staff, supplies, reagents, including any reference vaccine and materials, animals and equipment.

Under no circumstances will DCVMN International be held responsible or liable in any way for any claims, damages, losses, expenses, costs (planned or unforeseen) of each individual member of the Consortium required for the Project.

4. Project management

4.1 Identification

The Parties agree that the Project lead site is The Developing Countries Vaccine Manufacturers Network International (DCVMN Intl) established at Route de Crassier 7, 1262 Eysins-Nyon, Switzerland.

The Parties agree that the Project will be managed by Project Manager of DCVMN Intl. Switzerland ('Project Manager'). The Project Manager will report to a group established by the PSPT Consortium and made up of 5 experts ('the Steering Group'), one from the Italian Institute of Health, one from Intravacc, the statistician, 2 experts from DCVMN manufacturing companies of whole-cell Pertussis containing vaccines. Observers from WHO, Intravacc and NRA will be invited as well. The Observers are invited to participate in the meetings, but their presence is not mandatory; if they attend meeting, they can listen to the conversation, but they

are not expected to actively participate in the discussion and cannot vote or otherwise officially take part in decision making.

4.2 Responsibilities of the Project Manager

The Project Manager will have responsibility for the day-to-day management of the Project, with the Steering Group being concerned with overall policy and direction. The Parties agree that the Project Manager will have the following responsibilities:

- Interact with all the "Parties" through an ad hoc PSPT Consortium group and maintain open communication channels for interactions with the various laboratories in order to secure that the Project is carried out based on the agreed timelines; it might include the setting regular teleconferences and/or meetings for the Steering Group discussions in case of key scientific and technical questions;
- Interact with the "Parties" and provide with all the necessary procedures (SOPs) in collaboration with Intravacc;
- Interact with the Contract Manufacturing Organization and with Intravacc for the production, qualification and shipment of the coating antigen;
- Manage the "Project" activities and any other logistic activities in collaboration with DCVMN Intl. Secretariat;
- Manage any unexpected difficulties in the execution of the "Project" in collaboration with the PSPT Consortium and the Steering Group.

4.3 Responsibilities and activities of the Steering Group

The Steering Group will determine the overall nature of the Deliverables and will maintain responsibility for determining the technical standards to be adopted in the Project. The Steering Group will determine the scientific, technical and academic content of the Deliverables. The Steering Group will meet in person or virtually through teleconference at least four times a year. Additional meetings may be called by two or more Consortium Parties or on the advice of the Project Manager. The Steering Group may choose to take advice from third parties, if required. Meetings of the Steering Group will operate under the following rules:

- the Project Manager will notify the Steering Group members of the dates of meetings and outline the agenda with at least fourteen days' notice;
- each Steering Group member will have one vote, except the Chairman who has a casting vote in case of tie. However, a member may not vote on matters concerning a dispute with the Consortium where the member is the subject of the dispute;
- Steering Group members may nominate an alternate representative to attend meetings and vote on their behalf;
- decisions will be taken on the basis of a majority vote of those attending and eligible to vote;
- the minimum number of voting members required for meetings is three.

4.4 The responsibilities of the Chairperson

The Chair shall preside the Steering Group meetings, facilitate the discussions during the meetings, ensure every member has an opportunity to speak and is listen to; approve the agenda proposed by the Project Manager.

4.5 Responsibilities of the Consortium Participants

Each Party undertakes to use all reasonable endeavours, in line with the protocols or SOPs agreed upon, to:

- perform on time the tasks assigned to it under the schedules shown in Annex 3 [attached];
- participate actively with other Parties where necessary;
- promptly notify the Project Manager of any delay in performance;
- prepare and submit data to DCVMN Secretariat and present reports as required.

4.6 Changes in membership of the Consortium

Institutions may be invited to join the Consortium only by the unanimous decision of the Steering Group and on the condition that the new institution becomes a signatory Party to this Agreement. A Party may withdraw from the Consortium only in the event of irremediable breach of any Clause in this Agreement and with the unanimous agreement of the remaining Parties.

5. Data management

5.1 Data collection

In the course of the Project, each party is involved in the collection of data in the form of written reports biannually provided to DCVMN Intl. The data are to be sent to the DCVMN Secretariat and the Project Manager be notified. The data are stored in an archive at DCVMN Secretariat ('the PSPT Project digital Archive'). Each Party agrees to ensure that all laboratory data submitted to the DCVMN Secretariat are accompanied by documentation identifying the laboratory and date of origin/generation of data (for example ELISA reading results on May 8th, 2020 from Laboratory X), together, with any necessary ethical consent if non planned animal testing is performed in relationship with the Project. The Project Manager undertakes to ensure that all data stored in the PSPT Project Archive are referenced to the associated documentation stored as part of the PSPT Project digital Archive.

All the Consortium members will allow DCVMN to use their logos and some non-confidential information to be added to the PSPT Consortium webpage (part of the DCVMN website).

5.2 Data maintenance

The DCVMN Intl. Secretariat hereby undertakes to maintain the PSPT Project digital Archive for the duration of the Project and for a period of at least four years after the end of the Project. This period is subject to extension if the Steering Group so decides, and access to the data after this period will be decided by the Steering Group in due time.

6. Confidentiality

Each Party hereby undertakes to the other Party that it shall procure that its employees, agents and students shall:

- a. keep confidential all information of a confidential nature (whether written, oral or visual) concerning this agreement and the business affairs of any other Party that it shall have

obtained or received as a result of the discussions leading up to or entering into or performance of this agreement (the 'Information');

b. not without the prior written consent of the Party disclosing the information (Disclosing Party), disclose the Information, either in whole or in part, to any other person save otherwise to its employees, agents and students involved in the implementation or evaluation of the Project who have a need to know the same for the performance of their duties and are bound by equal or more stringent confidentiality terms as defined under this Agreement; and

c. to use the Information solely in connection with the implementation of the PSPT Project and not otherwise for their own benefit or the benefit of any third party.

The provisions a, b and c above shall not apply to the whole or any part of the Information to the extent that it can be demonstrated by the Party receiving the Information (Receiving Party) to be:

iv. Known to the Receiving Party prior to the date of this agreement and not obtained directly or indirectly from the Disclosing Party; or

v. Obtained from a third party who lawfully possesses such Information which has not been obtained in breach of a duty of confidence owed to the Disclosing Party; or

vi. In the public domain in the form in which it is possessed by the Receiving Party other than as a result of a breach of a duty of confidence owed to the Disclosing Party; or

vii. Required to be disclosed by legal process, law or regulatory authority, provided that the Receiving Party immediately notifies the Disclosing party its intent to disclose part or whole of the Information, and cooperate with the Disclosing Party either to limit the disclosure of Information or in obtaining an appropriate protective order preventing such disclosure.

Notwithstanding the foregoing, Parties are not obliged to share any information or data they deem reasonably related to manufacturing of the commercial antigen/vaccine batches, including any commercially sensitive information, know-hows or trade secrets.

Each Party hereby undertakes to the other Party to make all relevant employees, agents and students aware of the confidentiality of the Information and provisions of this Clause 6, and without prejudice to the generality of the foregoing, to ensure compliance by such employees, agents and students with the provisions of this Clause 6.

7. Intellectual property or ownership

7.1 Ownership

With regard to the ownership or intellectual property, the Parties agree as follows:

- all Deliverables (the collected data) by PSPT consortium,
- the Material (coating antigen only) used in the Project, shall be owned by DCVMN.

Each Party shall obtain the necessary assignments of intellectual property rights (this term includes, but is not limited to, copyright, database right, patents and trademarks) from all staff or agents involved in the development and production of the Deliverables on its behalf. Each Party warrants to the other Parties that it is the owner of the copyright and/or database rights



in the Deliverables or that it is duly licensed to use the Deliverables and that the content of the Deliverables used as contemplated in this Agreement does not infringe any copyright or other proprietary or intellectual property rights of any natural or legal person.

Each Party shall hold the other Parties harmless from and against any loss, damage, cost, liability or expense (including reasonable legal and professional fees) arising out of any actual or alleged infringement of such rights.

7.2 Marking

The Parties agree that all Deliverables shall be clearly marked identifying that the copyright is owned by the PSPT Consortium, i.e. signatories to this agreement. The Parties agree that the Steering Group will produce a suitable form of words acknowledging the involvement of the Parties and the ownership of the copyright, which shall appear on all copies of the Deliverables.

7.3 User rights

Each Party hereby grants to the other Parties and their affiliates a non-exclusive, indefinite, irrevocable, fully paid-up, royalty free license to use the Deliverable for research and other purposes, including commercial exploitation, after the completion of the Project.

8. Publication and press releases

Procedures for publications and press releases relating to the Project shall be agreed between the Parties through the Steering Group. Publication and press releases shall be subject to the respect of provision of Article 6 related to Confidentiality. No Publication and press releases shall be made except after giving an opportunity of review to the Parties, which in case of Publications shall be at least 30 days prior to its intended publication, and in case of press releases shall be at least 5 days prior to their public disclosure.

9. Liability

The work associated with the Project will be carried out by each Party in accordance with the highest scientific, academic, ethical and laboratory standards, and reasonable endeavours will be made to achieve the degree of reliability and accuracy appropriate to work of this kind. Each Party is solely responsible to take all precautions and obtain all insurances related to health, accident, travel, theft, injury and force majeure as the case may be during the performance of all activities related to the studies included in the Project. However, no Party has control over the use to which other Parties may put the results of the work, and each Party will therefore be deemed to have satisfied itself in every respect as to the suitability and fitness of the work for any particular purpose or application. To the extent permitted by law, no Party, its servants or agents accept any liability, however caused, arising from any error or inaccuracy in any opinion, advice, report or deliverable arising from this work nor for any resulting damage, loss expenses or claim, except to the extent that such can be shown to be caused by the willful negligence of the Party.

10. Administration

The Consortium shall be administered by the DCVMN Intl. Secretariat ("The Administrator"). However, contracts must be recommended for approval by the majority votes at Steering

Group and signed by the Executive Secretary or by the PSPT Project Manager at DCVMN International, after approval of its Executive Committee.

The Administrator of Consortium have all powers, privileges, and authority necessary to manage the affairs of the Consortium, to exercise any power common to the Consortium, and to work with each other to manage this project, having the Steering Group to deal with critical scientific advice. The Administrator shall also carry out the intent and purpose of this Agreement not inconsistent with law or this Agreement. These powers and responsibilities of the Administrator shall include general administrative duties which may arise from time to time, including, but not limited to:

- A. Setting financing policy and directing administrative principles for the Consortium.
- B. Evaluating and preparing required reports on the effectiveness of the Consortium and the Advancement of "In house validation studies".
- C. Assessing the training needs and interests of the consortium members and their respective staff.
- D. Providing long-term planning for the Consortium, if needed.
- E. Setting and evaluating program participation numbers and qualification of consortium representatives.
- F. Discussing collective purchases, supplies, equipment, rental/leases, etc., on behalf of the Consortium.
- G. Meeting periodically, as needed, to discuss issues associated with the Consortium.
- H. Other reasonable and necessary administrative duties.

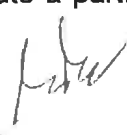
Approvals by the administrators may be accomplished by a consensus, a vote at a meeting, or by written affirmation by letter or electronic mail.

11. Miscellaneous

Assignment: No party will be entitled to assign this Agreement nor all or any of their rights and obligations hereunder without the prior written consent of the others, except that Parties may assign this Agreement, without such consent, to an entity that acquires all or substantially all of its business or assets to which this Agreement pertains, whether by merger, reorganization, acquisition, sale, or otherwise.

Disputes/arbitration: All disputes or differences which will at any time hereafter arise between the Parties in respect of the construction or effect of this Agreement or the rights, duties and liabilities of the Parties hereunder, or any matter or event connected with or arising out of the Project, will be referred in the first instance to the Steering Group. If the Steering Group is unable to resolve the dispute, the Chair of the Steering Group shall select an independent third party to act as arbitrator.

Relationship: Nothing in this Agreement will create or be deemed to create a partnership or the relationship of employer and employee between the Parties.



This Agreement may be amended. Any amendment or addition to this Agreement shall not have any effect unless made in writing and signed by all parties.

Law and jurisdiction: This Agreement will be governed by the laws of Switzerland. This Agreement is subject to the exclusive jurisdiction of the Swiss courts to which the parties hereto submit.

Indemnity: Each Party represents and warrants to the other Parties that publication or distribution of those parts of the Deliverables that it has contributed will not contravene any laws, including but not limited to the laws of defamation and contempt of court (or concepts approximating thereto).

The signing of this Consortium Agreement is not a formal contractual undertaking and not legally binding. It implies that the signatories will strive to reach the objectives stated in the Consortium Agreement, to the best of their ability. In this respect each party to this Consortium Agreement waives any and all rights of recourse it may have against the other parties under this Consortium Agreement or at law.

AGREED BY THE PARTIES through their authorised signatories

For and on behalf of The State of the Netherlands, represented by the Minister of Public Health, Welfare and Sports, on behalf of the Minister, Projectdirectie ALT, The Institute for Translational Vaccinology (Intravacc):

..... Date

Name:

For and on behalf of THE NATIONAL CONTROL LABORATORY OF THAILAND:

..... Date

Name:

For and on behalf of NATIONAL QUALITY CONTROL LABORATORY OF INDONESIAN FOOD AND DRUG AUTHORITY:

..... Date

Name:

For and on behalf of SERUM INSTITUTE OF INDIA PVT LTD:

..... *Sy an roke* Date *02.07.2020*

[Signature]

Name: SUNIL GAIROLA

For and on behalf of BIOLOGICAL E LIMITED:

..... Date

Name:

For and on behalf of BHARAT BIOTECH INTERNATIONAL LIMITED:

..... Date

Name:

For and on behalf of PASTEUR INSTITUTE OF INDIA:

..... Date

Name:

For and on behalf of BIO FARMA OF INDONESIA:

..... Date

Name:

For and on behalf of PANACEA BIOTEC LIMITED OF INDIA:

..... Date

Name:

For and on behalf of SANOFI HEALTHCARE INDIA PRIVATE LIMITED:

..... Date

Name:



For and on behalf of BULBIO-NCIPD LTD:

..... Date

Name:

For and on behalf of DCVMN International:

 Date *26 August 2020*

Name: *SONIA PAGLIUSI*.....

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ANNEX 1

DCVMN Proposal to NIIMBL - Project Call 3.1G

International in-house validation of the Pertussis Serological Potency Test (PSPT) in mice to replace the in vivo challenge Mouse Protection Test in whole-cell Pertussis (wP) vaccine batch testing.

PI: DCVMN International

Abstract

Whole-cell Pertussis (wP) containing vaccines are widely used for routine vaccination of children in several parts of the world as part of various combinations of vaccines in childhood immunization programs.

The standardization and control of wP vaccines was addressed by Kendrick in the 1930s, who developed a mouse protection assay involving intracerebral challenge with a lethal dose of the *Bordetella pertussis* to assess vaccine potency based on immunized animal survival in the period of two weeks after challenge. This Mouse Protection Test (MPT) or Kendrick Test shows high variability, poor reproducibility, difficulties in statistical validity, requiring use of extensive numbers of animals which experience severe pain and distress. This project aims to support in-house validation of a serological assay (Pertussis Serological Potency Test - PSPT) to enable the transition from intracerebral challenge to immunization, to assess the potency of wP containing vaccines *in vitro*, to reduce variability of the test, the numbers of animals and the level of distress. The PSPT was evaluated in mice and guinea pigs favourably in published studies allowing for discrimination of vaccine batch potency and use of the test for demonstration of consistency in production. Hence, in-house validation of PSPT is now a critical step.

Executive Summary

International *in-house* validation of the Pertussis Serological Potency Test (PSPT) in mice to replace the *in vivo* challenge Mouse Protection Test in whole-cell Pertussis (wP) vaccine batch testing.

Whooping cough or Pertussis is a highly contagious respiratory disease caused by the bacterium *Bordetella pertussis*. Before the availability of vaccines, pertussis was a frequent cause of morbidity and mortality, particularly in infants and young children.

The introduction of pertussis-containing vaccines into the immunization schedule of infants and children has reduced pertussis incidence worldwide, although sporadic outbreaks, even with mortality, remain relatively common in case of poor vaccination coverage.

The whole-cell Pertussis (wP) vaccine was developed more than a century ago, and it is still largely used in developing countries because of its proven efficacy and long-lasting immunity, although the vaccine also induces more frequent side-effects than the acellular Pertussis vaccine.